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Preterm Infant Growth and Human Milk Exposure in the NICU

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PRETERM INFANT GROWTH AND HUMAN MILK EXPOSURE IN THE NICU

by

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ABSTRACT

PRETERM INFANT GROWTH AND HUMAN MILK EXPOSURE IN THE NICU

by

Lindsay K. Schehr

University of Wisconsin-Milwaukee, 2018
Under the Supervision of Teresa S. Johnson, PhD, RN

Purpose: Examine how feeding practices impact growth in infants less than 1500 grams from birth until reaching full enteral feedings. Identify growth velocity rates associated with clinician initiation of fortification of preterm infant human milk feedings.

Design: Retrospective descriptive study

Setting: Level three neonatal intensive care unit in a small urban community in Southeast Wisconsin**.**

Participants: A convenience sample of 82 very low birth weight preterm infants who were born with birth weight < 1500 grams, vaginal or cesarean birth, born at study hospital or transferred to study hospital within 12 hours of birth.

Methods: Data were collected from the participant's electronic health records from birth until the infant reached full enteral feedings.

Results: 82 preterm infants with a mean gestational age 29.30 weeks (SD 3.11) and mean birthweight 1108.84g (SD 272.77) were included. In those infants that received fortification of mother's own milk and/or pasteurized donor human milk (53.7%), mean growth velocity was 3.89 gm/kg/day (SD 12.76) and mean volume of enteral intake was 132.60 mL/kg/day (SD 28.29). When reaching full feeding, mean growth velocity was 0.15 gm/kg/day (SD 11.09).

Conclusions: Initiation of human milk fortification or lactoengineering earlier in development may have prevented or decreased extent of growth failure as evidenced by growth velocity less than 15 gm/kg/day when reaching full enteral feedings.

DEDICATION

First and foremost, I would like to thank my husband, AJ, standing behind me during every struggle and each success. Thank you for wearing all hats. You carried me through the last 3 years. You were as important to finishing this degree as I was. You made all the difference in my success.

To my children, Noah, Zac, and Amelia, thank you for your patience and unconditional love. You give me energy and strength. You remind me daily of all that is yet to be.

To my mom, Cheryl, you never doubt me, even in times I doubt myself, thank you.

To my family, thank you for your endless encouragement, support, and love along this journey.

To Dr. Teresa Johnson, thank you for serving as my mentor, teacher, and friend for the last 3 years. Our story is unlike any other, from Amelia to world travels, thank you for your guidance and support. You have inspired me to imagine a world where it is possible for all children to access optimal nutrition: human milk. Your encouragement and enthusiasm has inspired to use nursing research and practice to make this achievement a reality.

To my dissertation committee, Drs. Michele Polfuss, Kris Barnekow, and Sandeep Gopalakrishnan, thank you for your valuable insight and most precious gift of time.

I am exiting this doctoral program with many friendships, an expanded mind, a full heart, and greater sense of what I am capable of. “She believed she could, so she did.”

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1: Introduction

Background

Most health care providers guided by the American Academy of Pediatrics (AAP) strive to prescribe nutritional practices in the neonatal intensive care unit (NICU) to achieve growth comparable to intrauterine life (Hay, 2013; Kleinman & AAP, 2009; Puntis, 2006). The recommended standard intrauterine growth rate is 15 gm/kg/day (Kleinman & AAP, 2009). Intrauterine growth is accepted as the standard for preterm extrauterine growth because a superior growth standard remains undefined (Fenton & Kim, 2013).

After a preterm infant regains initial weight loss from birth, weight gain at the recommended growth velocity of 15 gm/kg/day can still result in growth failure (Martin et al., 2009; Reali et al., 2015; Ruth, 2008). Martin et al. (2009) categorized growth failure as weight less than the 10th percentile for postmenstrual age on a standardized intrauterine growth chart. Martin et al. (2009) reported that when the study infants exceeded the growth velocity of 15 gm/kg/day, growth failure still occurred in 75% of the 1,187 infants studied.

Nutrition management to produce adequate growth of preterm infants remains one of the most challenging aspects of care. The types, amounts, and frequencies of feedings during the initial hospitalization have important implications for future infant growth and development of preterm infants. The estimated nutritional requirements for preterm infants are driven by nutrient accretion and growth of a third trimester fetus in attempt to mirror the intrauterine growth standard (Tudehope, 2013). The resulting recommendations for nutritional requirements, including macronutrient and micronutrient intake, are based primarily on expert opinion to reach a growth standard that may not be optimal (Tudehope, 2013). This leads to continued controversy among health care providers regarding optimal prescribed feedings.

Human milk is regarded as the superior and preferred feeding method for hospitalized preterm infants (Menon & Williams, 2013). However, significant controversy continues how human milk should be provided or fortified or lactoengineered to support optimal growth (Menon & Williams, 2013). For infants whose mothers cannot provide breastmilk, infants may be fed pasteurized donor human milk (PDHM), which they should receive, at minimum, until 34 weeks corrected gestational age or 28 days of life (Parker, Barrero-Castillero et al., 2013). Despite the known benefits of exclusive human milk feedings, many health care providers caring for preterm infants supplement human milk with bovine milk-based fortifier and/or formula to provide additional protein, calories, and other nutrients to try to maximize growth acceleration (Menon & Williams, 2013).

Growth failure among preterm infants has consequences for short- and long-term health. Preterm infant growth failure is associated with adverse neurodevelopmental outcomes and somatic development, longer NICU stay, and potentially preventable morbidities (McLeod & Sherriff, 2007; Vasu & Modi, 2007; Walker, Keene, & Patel, 2014). Growth failure can contribute to impeded brain growth resulting in irreversible neurodevelopmental deficits, including abnormal motor and cognitive function (Butler, Szekely, & Grow, 2013; McLeod & Sherriff, 2007; Walker et al., 2014). Growth failure in preterm infants and subsequent infant catch-up growth is related to increased risk for disease in adulthood, including decreased insulin sensitivity, increased insulin resistance, altered adipose tissue metabolism (Finken et al., 2006), obesity, and hypertension (Thomas et al., 2011). The risks associated with growth failure or contrary rapid catch-up growth has potential health implications that must be weighed heavily when evaluating goal growth standards among preterm infants.

As preterm infants are not a homogenous group, a major conceptual flaw is created when using a standard growth rate to define optimal growth (Embleton, Cleminson, & Zalewski, 2017). Preterm infant growth is multifactorial based on maternal, fetal, and infant physiological, developmental, genetic, nutritional, and environmental factors that differ in each preterm infant. As these variables differ among preterm infants, it is apparent that an intrauterine rate of growth for one infant may be sufficient, but a slower trajectory may be more appropriate and biologically plausible for the next infant (Embleton et al., 2017).

Problem Statement

It is unclear what combination of neonatal nutrition is most highly associated with optimal preterm infant health, growth, and development (Rice & Valentine, 2015). Supplementation of human milk is often quickly and frequently performed in NICUs with bovine fortification and/or formula to reach a growth standard that may not be appropriate (Menon & Williams, 2013). Nutritional management of preterm infants is marked by a lack of practice uniformity (Wight et al., 2008). Heterogeneity of nutrition practices can be seen in every aspect of nutritional management from the first hour of life to NICU discharge (Wight et al., 2008). There is lack of evidence to demonstrate that it is optimal or safe to set the goal of extrauterine growth of preterm infants to mimic intrauterine growth (Pereira-da-Silva & Virella, 2014). Comprehensive and multidisciplinary nutritional monitoring associated with growth outcomes is not consistent in NICUs (Wight et al., 2008).

Target Population and Rationale

The target population is preterm infants born less than 37 completed weeks gestation and weighing less than 1,500 grams. A preterm infant is defined as born at less than 37 completed weeks gestation (Mosby, 2006). The target population is considered very low birth weight

(VLBW). Very low birth weight infants are defined as infants born at less than 1,500 grams (Wight et al., 2008). Survival rates of VLBW infants have improved; therefore, more attention needs to be focused on the quality of survival through optimal nutrition management (McLeod & Sherriff, 2007; Thoyre, 2007).

Purpose of the Study

The purpose of the this study is to examine how feeding practices impact growth in infants less than 1500 grams from birth until reaching full enteral feedings.

Primary Research Aims

1. Understand how the type and amounts of feedings are associated with preterm infant growth during the initial birth hospitalization.
2. Identify growth velocity rates associated with clinician initiation of fortification of preterm infant human milk feedings.

Research Questions

Primary Research Questions

1. What is the growth velocity (gm/kg/day) of VLBW preterm infants at the time human milk fortification is initiated?
2. Is there a relationship between growth velocity (gm/kg/day) of VLBW preterm infants from birth to full feeding and percentage of human milk intake?
3. Is there a relationship between growth velocity (gm/kg/day) of VLBW preterm infants from birth to full feeding and percentage of mother's own milk, pasteurized donor milk, and mixed donor/mother's own milk intake?

Secondary Research Questions

1. What is the volume of enteral intake (mL/kg/day) at the time human milk fortification is initiated?
2. What is the average day of life when birth weight is regained?
3. When full feedings are achieved, on average, how many kilograms is the infant from birth weight?
4. What is the average day of life that enteral feedings are initiated?
5. What percentage of infants experience suboptimal growth, as measured by a growth velocity < 15 gm/kg/day, when reaching full feedings in the NICU?

Conceptual Framework

A comprehensive conceptual model or theory appropriate to guide research of preterm infant growth failure in the NICU was not identified in the literature. As foundational work, this writer has created a physiological preterm infant growth model based on frequently associated concepts and variables (see Figure 1). Scientists and clinicians attempt to understand these conceptual relationships by building research and practice from a theoretical perspective. Conceptualization and theory are needed to systematically expand nursing discipline's knowledge (Meleis, 2007). By examining the phenomena of preterm infant growth and nutrition from a theoretical lens, we can categorize what is known of phenomena, indicate gaps in nursing knowledge, and point out where further knowledge should be developed. The frequently associated physiological concepts seen repeatedly in the literature to define and describe preterm infant growth and nutrition were used to create the Physiological Preterm Infant Growth Model.

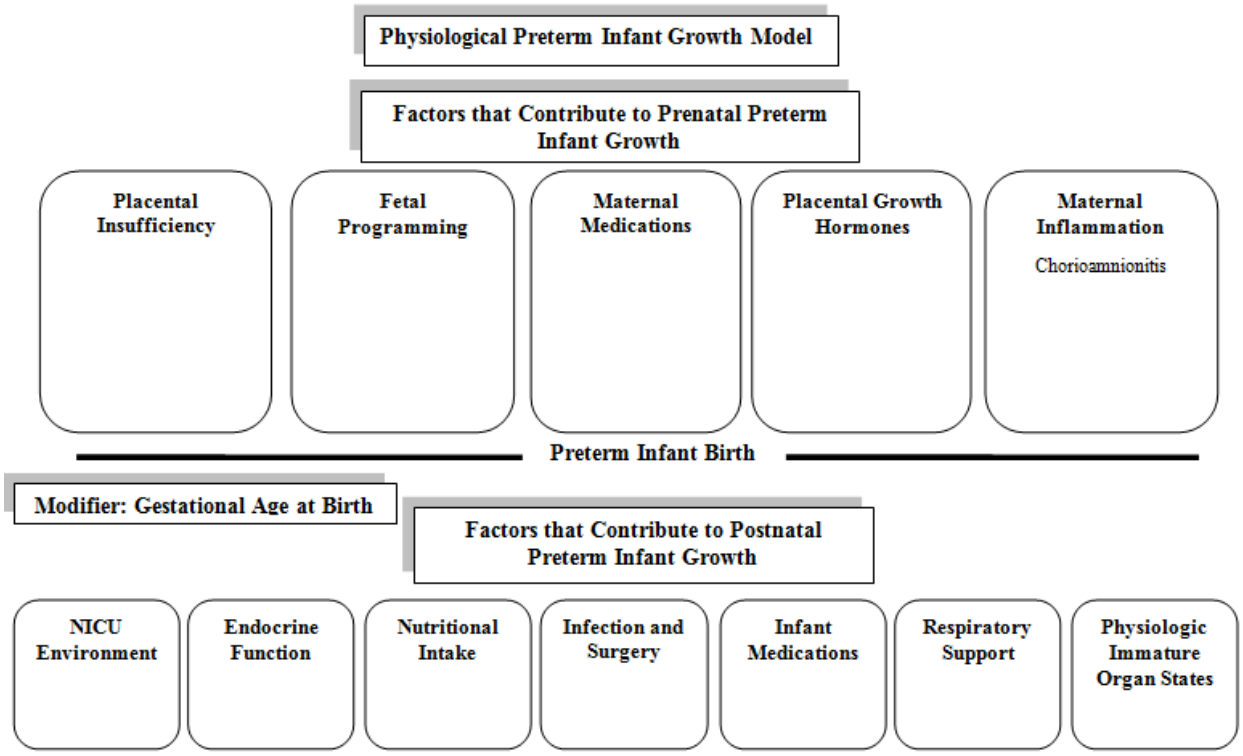

Figure 1. Physiological Preterm Infant Growth Model.

The Preterm Infant Physiological Growth Model is considered a practice-based framework. Meleis (2012) argues that practice-based frameworks are appropriate when theories do not exist or are not useful to describe the phenomena or population. When current theoretical material does not translate into practice or is not relevant to the phenomena, it may be appropriate to inductively develop the framework (Meleis, 2012). This model provides clear, identifiable and measurable variables to define optimal growth and to explain the physiologic complexity of factors that can interfere with optimum preterm infant growth.

There are multiple systems that impact a preterm infant's intrauterine and extrauterine growth. There is a dynamic interaction between maternal, fetal, and infant physiological, developmental, genetic, nutritional, and environmental factors that influences preterm infant growth. As the biological foundations and risk factors identified in the Physiological Preterm

Infant Growth Model vary, it is apparent that an intrauterine rate of growth may not be biologically plausible for all preterm infants (Embleton et al., 2017). The Preterm Physiological Growth Model provides a foundation to explain that preterm infants are not homogenous in their risk for growth outcomes and demonstrates that the current growth standard is conceptually flawed. The Physiological Preterm Infant Growth Model provides foundational concepts to inform the association of nutritional support and infant growth in this dissertation. The concepts, as explained in the Physiological Preterm Infant Growth model, have influenced understanding of salient components of preterm infant growth as a phenomenon. This model guided investigation to solidify the definition of growth failure in hospitalized preterm infants through concept analysis further discussed in Chapter 2. The Physiological Preterm Infant Growth Model will require continued development in the future.

Significance

Preterm infant birth is the second leading cause of mortality worldwide (Partnership for Maternal, Newborn, and Child Health, 2011). In 2015, approximately 3,977,745 births were reported in the United States (Hamilton, Martin, & Osterman, 2016). Of these births, 55,290 (1.39%) were considered VLBW (Hamilton et al., 2016). Very low birth weight preterm infants who survive commonly experience growth deficiency (Steward, 2012). Approximately 90% of VLBW infants are considered growth restricted, falling below the 10th percentile on a standardized intrauterine growth curve, by 36 weeks gestational age (Dusick, Poindexter, Ehrenkranz, & Lemons, 2003).

Assumptions

Assumptions for this study were that the types of preterm infant nutritional practices are a determinant of growth. Further, it was assumed that the type of nutritional practice would predict the relationship between study variables.

Structure of Dissertation

This dissertation is comprised of six chapters, within which are three manuscripts accepted and/or readied for publication. Chapter II presents manuscript one, "A Concept Analysis of Growth Failure in Preterm Infants in the NICU," used to examine the fundamental elements and to provide an operational definition of the concept of growth failure in preterm infants in the NICU. Chapter III provides a review of literature on preterm infant growth and nutrition. Chapter IV presents the research methodologies and study design. Chapter V presents manuscript two, "Preterm Infant Growth and Human Milk Exposure in the NICU," used to present and discuss study results. Finally, Chapter VI discusses implications to nursing research, practice, and policy; and presents manuscript three, "The Political Imperative of an Exclusive Human Milk Diet."

Chapter II: Conceptual Analysis

After construction of the Physiological Preterm Infant Growth Model, the next conceptual step in this dissertation was to examine the specific concept and definition of preterm infant growth. The current state of the science on preterm infant growth did not provide researchers or clinicians with sufficient literature to determine optimal growth for preterm infants (Embleton et al., 2017). The literature review revealed it is apparent that the same rate of growth is not biologically plausible for all preterm infants (Embleton et al., 2017). Considering there is lack of consensus on what appropriate growth is, it was then a reasonable step to conceptualize what growth is not.

Conceptualization is critical to defining, describing, clarifying, explaining, and understanding phenomena (Meleis, 2007). Ultimately, conceptual analysis provides a sound organization of concepts, clarifies vague phenomena, and provides a symbolic representation of reality to support the concept's theoretical basis (Walker & Avant, 2011). Through conceptual analysis, an operational definition of growth failure in preterm infants in the NICU was constructed.

In the following section of Chapter II is a manuscript published in the *Journal of Obstetric Gynecologic and Neonatal Nursing*: "A Concept Analysis of Growth Failure in Preterm Infants in the NICU." This publication was available online October 2017 and in print November/December 2017. "A Concept Analysis of Growth Failure in Preterm Infants in the NICU" was created utilizing Walker and Avant's (2011) steps to concept analysis as foundational work for this dissertation.

Concept Analysis of Growth Failure in Preterm Infants in the NICU

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ABSTRACT

Growth failure has not been consistently defined for preterm infants, which contributes to unclear clinical guidelines for optimal growth and development. Therefore, the purpose of this concept analysis was to identify all uses and attributes of the concept, present model and contrary cases, identify antecedents and consequences, define empirical referents, and provide an operational definition of growth failure among preterm infants in the NICU.

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Facilitating preterm infant growth is a complex process that influences morbidity and mortality of infants. *Preterm birth* is defined as birth before 37 completed weeks of gestation, and it is the second leading cause of infant mortality worldwide (World Health Organization, 2016). In 2015, 3,978,497 births were registered in the United States, including 383,129 (9.63%) preterm births (Martin, Hamilton, Osterman, Driscoll, & Matthews, 2017). Of these infants, 321,065 (8.07%) were classified as low birth weight, and 55,699 (1.40 %) were classified as very low birth weight (Martin et al., 2017). The risk and extent of growth failure of preterm infants during initial hospitalization increases with decreasing gestational age and birth weight (Gleason & Devaskar, 2011). Very-low-birth-weight preterm infants who survive commonly experience growth deficiency (Steward, 2012). Approximately 90% of very-low-birth-weight infants experience growth restriction and fall below the 10th percentile on a standardized premature infant growth chart by 36 weeks corrected gestational age (Dusick, Poindexter, Ehrenkranz, & Lemons, 2003). Preterm infants born before 28 weeks gestation are commonly hospitalized until 37 to 40 weeks corrected gestational age (Martin et al., 2009). However, by 40 weeks corrected gestational age, most preterm infants weigh less than a third-trimester fetus at the same gestational age (Martin et al., 2009). The decreased weight of preterm infants is problematic because most clinicians practice under the premise that if growth failure in hospitalized preterm infants is not identified and treated, these infants will be at increased risk for adverse neurodevelopmental outcomes, longer NICU stays, and potentially preventable morbidities (Butler, Szekely, & Grow, 2013; McLeod & Sherriff, 2007; T. C. Walker, Keene, & Patel, 2014).

Growth failure in preterm infants has not been consistently defined, which contributes to unclear clinical guidelines for optimal growth and development. Therefore, the purpose of this concept analysis was to examine the fundamental elements and provide an operational definition of the concept of growth failure in preterm infants in the NICU. L. O. Walker and Avant's (2011) conceptual analysis method was used to guide concept selection, determine the purpose of the analysis, identify all uses, define the attributes, present a model and a contrary case, identify antecedents and consequences, and define empirical referents of preterm infant growth failure.

Uses of Growth Failure in Preterm Infants in the NICU

All uses of the concept were identified through exploration of definitions, applications, and uses across disciplines. Medical dictionary definitions

and medical subject headings (MeSH) were examined, and a literature search was completed of electronic databases. Separate definitions for *premature infant* and *growth failure* are provided in Mosby's (2006) medical dictionary. *Premature infant* is defined as "any neonate, regardless of birth weight, born before 37 weeks gestation" (p. 1513). *Growth failure* is defined as "a lack of normal physical and physiologic development that results from genetic, nutritional, pathologic, or psychosocial factors" (p. 836).

Medical Subject Headings

MeSH terms and definitions are used in bibliographic searches, literature reviews, and examination of the current state of science. The search term *preterm infant growth failure,* as a single term, was not found in MeSH. The single terms *preterm* and *growth failure* were not found in MeSH. The terms *infant* and *premature infant* were defined separately. The U.S. National Library of Medicine (2017) defined *infant* as a child between 1 and 23 months of age and *premature infant* as a human infant born before 37 weeks gestation.

Definitions in the Published Literature

MEDLINE, CINHAL, and ScienceDirect electronic databases were searched for articles published from 1990 to the present using the keywords *premature*, *preterm*, *premature infant*, *infant*, *growth,* and/or *preterm infant growth failure.* The literature search was expanded broadly to include the disciplines of nursing, medicine, nutrition sciences, biology, and physiology. Articles were included if the concept preterm infant growth failure was defined, described, or used. No published concept analysis on preterm infant growth failure was found. Preterm infant growth failure was used as a physiologic measurement to describe how nutritional practices influence growth as a biological condition and a predictor of health.

Physiologic Measurement

Preterm infant growth failure was frequently defined in terms of physiologic outcomes. The most common physiologic outcome of preterm growth failure was defined using anthropometric measurements and growth velocity plotted on a growth chart. Anthropometric measurements, including weight, length, and head circumference, are plotted on a standardized growth chart during the NICU stay (Greer & Olsen, 2013; McLeod & Sherriff, 2007). Clinicians use growth charts in the NICU to document a visual display of growth over time. Although multiple growth charts have been developed to monitor infant growth, the two primary types of growth charts used to evaluate preterm infant growth in the NICU are growth reference charts and growth standard charts.

Growth failure in preterm infants has not been consistently defined, which contributes to unclear clinical guidelines for optimal growth and development.

Growth reference charts are descriptive and represent how a population is growing (Villar et al., 2010). Growth reference charts are created based on statistical summaries of anthropometric measurements of a reference group (Villar et al., 2010). Growth reference charts include fetal estimation curves, birth weight for gestational age charts, and postnatal longitudinal growth charts (Villar et al., 2010). Fetal estimation curves are based on fetal ultrasonographic anthropometric measurements across multiple gestational ages (Villar et al., 2010). Birth weight for gestational age charts represent actual growth of infants constructed from a single anthropometric measure of weight obtained at birth across multiple different gestational ages (Villar et al., 2010). Postnatal longitudinal growth charts represent actual postnatal growth from a reference group over time (Villar et al., 2010). Growth reference charts describe anthropometry of the population but do not account for environmental, nutritional, socioeconomic, and health conditions (Bertino, Milani, Fabris, & De Curtis, 2007).

In contrast, growth standard charts define how a population should be growing in optimal nutritional and environmental conditions, as opposed to how they have grown during a specific time and place (Giuliani et al., 2016; Villar et al., 2010). Growth standard charts represent longitudinal monitoring of prospective healthy growth (Villar et al., 2010). However, growth standard charts do not inform preterm infant growth assessments until infants reach postmenstrual age greater than or equal to 37 weeks (Fenton & Kim, 2013). *Postmenstrual age* is defined as gestational age plus chronologic age after birth (Engle, 2004).The 2013 Fenton Preterm Growth Chart, a growth reference chart, is one of the most widely used growth charts to monitor preterm infant growth in the NICU (Fenton & Kim, 2013). This growth chart combines fetal growth patterns based on weight

for gestational age for preterm infants combined with the World Health Organization Growth Standards of term infants (Fenton & Kim, 2013). The strength of the 2013 Fenton Preterm Growth Chart is that it provides a single tool with which to assess how an infant grew while in the uterus based on birth weight and then is used to monitor postnatal growth to and beyond term (Pereira-da-Silva & Virella, 2014).

Most health care providers, guided by the American Academy of Pediatrics, strive to prescribe nutritional practices in the NICU to achieve growth comparable to intrauterine life (Hay, 2013; Kleinman, 2008; Puntis, 2006). Intrauterine growth is commonly used as the standard for extrauterine growth of preterm infants because a superior growth standard remains undefined (Fenton & Kim, 2013). However, there is a lack of evidence to show that it is optimal or safe to set the goal of extrauterine growth of preterm infants to mimic intrauterine growth (Pereira-da-Silva & Virella, 2014). Intrauterine growth commonly reflects an ideal growth pattern that is rarely achieved in preterm infants (Horemuzova, Söder, & Hagenäs, 2012).

Preterm infant growth failure is frequently defined as weight less than the 10th percentile for postmenstrual age on a standardized growth chart at discharge from the NICU (Martin et al., 2009; McLeod & Sherriff, 2007; Ruth, 2008). Growth velocity is calculated as increase in grams per kilogram per day (Greer & Olsen, 2013; Patel, Engstrom, Meier, Jegier, & Kimura, 2009) and increase in centimeters per week in head circumference and length (Greer & Olsen, 2013). Growth failure in preterm infants is associated with growth velocity rates less than 15 g/kg/day in weight, 0.5 cm/week in head circumference, and/or 1 cm/week in length (Greer & Olsen, 2013). Even after a preterm infant regains initial weight loss from birth, weight gain at the recommended growth velocity of 15 g/kg/day will result in failure to return to birth weight percentile when plotted on a standard preterm infant growth chart (Martin et al., 2009; Reali et al., 2015; Ruth, 2008). Martin et al. (2009) reported that even when the study infants exceeded the growth velocity of 15 g/kg/day, growth failure occurred in 75% of the 1,187 infants studied. Reali et al. (2015) reported that despite an average growth velocity of 16.04 g/kg/day in preterm infants during their hospitalizations, 72.3% weighed less than the 10th percentile on a standard preterm infant growth chart at discharge from the hospital. Health care providers do not unanimously agree that growth velocity of 15 g/kg/day is an appropriate or sufficient goal to prevent growth failure in preterm infants (Fenton & Kim, 2013).

How Nutritional Practices Influence Growth

The types of nutrition that preterm infants may receive include total parenteral nutrition (TPN), mother's own milk, donor human milk, fortified human milk, and formula (Colaizy, Carlson, Saftlas, & Morriss, 2012). Variations in feeding practices such as timing of introduction, type, and amount of nutrition can contribute to growth failure in preterm infants (Hay, 2013; Su, 2014). Hay (2013) reported that the nutritional intake of preterm infants may fall below that required for optimal growth for many reasons:

- Delay in starting TPN or providing very low amounts of TPN for multiple days.
- Delay of enteral feeding, possibly for days because of concerns about an immature gut and possible intolerance of feedings.
- Once TPN is started, nutrient intake may be provided at less than the intrauterine rate and slowly increased. As a result, multiple days may pass before the appropriate nutrient amounts for gestational age are reached.
- Use of diluted nutritional mixes including unfortified mother's own milk or unfortified donor milk.
- After feedings are started, changes in the preterm infant's condition may cause intravenous or enteral feedings to be withheld.

Although human milk is the superior and preferred food for preterm infants (Arslanoglu, Moro, & Ziegler, 2006; Boyd, Quigley, & Brocklehurst, 2007; Cristofalo et al., 2013; McLeod & Sherriff, 2007; Ruth, 2008), human milk alone may not always meet the greater nutrient needs of preterm infants without fortification or lacto-engineering (Schanler, Lau, Hurst, & Smith, 2005). Some researchers reported that the use of fortified human milk can improve short-term weight gain and growth velocity and increase linear growth (Hair et al., 2014). McLeod and Sherriff (2007) and Reali et al. (2015) argued that in order for preterm infants to be able to achieve optimal growth velocity, human milk used for feedings requires targeted fortification. Fortification of human milk provides increased protein and is correlated with growth velocity that exceeds the expected growth

velocity of 15 g/kg/day (Reali et al., 2015; Rochow et al., 2013). Engineering human milk with a human-derived cream supplement using the creamatocrit technique can provide energy-dense feedings without substantial increase in the total volume of feedings (Hair et al., 2014).

Nutritional experts recommended nutrient intake of at least 2 to 3 g/kg/day protein and 1 to 2 g/kg/day lipid for the first 2 days of life (Embleton & Tinnion, 2009). By the first week of life, the recommended intake is 3.8 to 4.0 g/kg/day for protein, 3.0 to 3.5 g/kg/day for lipids, and 120 kcal/kg/day for calories (Embleton & Tinnion, 2009; Iacobelli et al., 2015). Human milk that is not fortified or lacto-engineered is considered deficient in the recommended amounts of at least one or a combination of these macronutrients (Rochow et al., 2013).

Controversy continues about how preterm infant nutrition should be provided (from the breast, fortified, or lacto-engineered) to prevent growth failure. Although some of the nutritional deficits that preterm infants experience are a result of metabolic limitations, many may occur because of clinical practices that limit nutritional intake and lack a strong evidence base (Embleton & Tinnion, 2009).

Biological Condition

Growth failure in preterm infants is characteristic of biological conditions with consequences. Although we commonly consider nutrition as the cause of growth failure in preterm infants, conditions including genetic acquired diseases, liver disease, endocrine abnormalities, surgery, infections, sepsis, ventilator dependence, respiratory distress, persistent pulmonary dysfunction, hypothermia, cold stress, and postnatal exposure to dexamethasone are also contributors (Bartholomew et al., 2013; Hay, Brown, & Denne, 2014; Vinall et al., 2012). Second, the drugs used to treat biological conditions can negatively affect infant nutrient metabolism and growth (Hay, 2013).

Predictor of Health

Finally, growth failure in preterm infants is a predictor of short- and long-term health and is associated with health problems, including physiologic instability (apnea and poor thermoregulation), limited endurance, poor suck/swallow/breathe coordination, impaired swallowing, and poor oral motor control (Barlow, 2009). Growth failure in preterm infants can contribute to impeded brain growth and result in neurodevelopmental deficits (Butler et al., 2013; Embleton & Tinnion, 2009; McLeod & Sherriff, 2007; T. C. Walker et al., 2014). The mechanisms that cause accelerated catch-up growth in a preterm infant who has experienced growth failure during hospitalization may increase risk for disease in adulthood, including obesity and obesity-associated morbidities (Thomas et al., 2011).

The attributes of growth failure in preterm infants in the NICU are suboptimal physiologic growth, insufficient nutritional support, and excessive energy expenditure.

Attributes

The goal of defining attributes of growth failure in preterm infants is to identify the most frequently associated characteristics of the concept that are seen repeatedly and help differentiate the occurrence of the specific concept from a similar concept (L. O. Walker & Avant, 2011). The attributes of growth failure in hospitalized preterm infants are suboptimal physiologic growth, insufficient nutritional support, and excessive energy expenditure. The attributes of growth failure in preterm infants are summarized in Figure 1.

Suboptimal Physiologic Growth

The physiologic growth parameter used to measure growth failure in preterm infants is *suboptimal growth*. Suboptimal growth is measured by examining growth velocity on a standard preterm infant growth charts. *Suboptimal growth* is defined as growth velocity less than 15 g/kg/day or weight less than the 10th percentile for postmenstrual age on a standard preterm infant growth chart (Martin et al., 2009; McLeod & Sherriff, 2007; Ruth, 2008).

Insufficient Nutritional Support

Growth failure in preterm infants can potentially occur because of insufficient nutritional support. Insufficient nutrition is inadequate parenteral and/or enteral nutrition that results in weight less than the 10th percentile for postmenstrual age on a standard preterm infant growth chart at discharge from the NICU. Insufficient nutritional support can be caused by infrequent feeding; ineffective feeding, including poor breast latch and feeding intolerance; or nutrient-deficient milk that does contain the recommended amounts of macronutrients for daily intake (Embleton & Tinnion, 2009; Iacobelli et al., 2015).

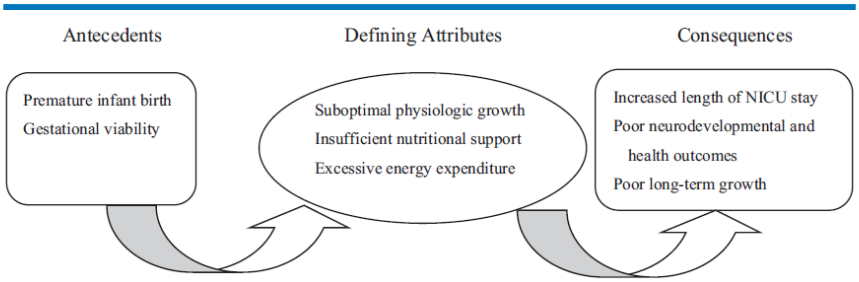

Figure 1. Conceptual map of growth failure in hospitalized preterm infants.

Excessive Energy Expenditure

Excessive energy expenditure caused by environment factors, biological conditions, and morbidities is a critical component of growth failure in preterm infants. The complex interaction of stressors impedes growth. Stressors include genetic acquired conditions, surgery, infection, ventilator dependence, respiratory distress, persistent pulmonary dysfunction, hypothermia, hypoglycemia, cold stress, and postnatal exposure to medications that affect nutrient metabolism (Bartholomew et al., 2013; Hay et al., 2014; Vinall et al., 2012).

Constructed Cases

Model Case

A preterm male infant was born at 31 0/7 weeks gestation. At birth, the infant weighed 1,020 g, was 37 cm long, and had a head circumference of 26.25 cm; these measurements were at the 6th, 8th, and 7th percentiles, respectively, on the Fenton Growth chart. At birth, the infant received surfactant and was subsequently intubated for respiratory support. A solution of 5% dextrose in water was immediately started on an intravenous umbilical line. Total parenteral nutrition with 10% amino acids, 10% dextrose, and 20% lipids was started at 4 hours of life. No expressed or donor breast milk was available. On Day of Life 2, enteral feedings were given with 24-calorie preterm infant formula. Feedings were administered every 4 hours. On Day of Life 18, the NICU staff noticed that the infant had a distended abdomen, palpable loops of bowel, temperature instability, lethargy, and one episode of bilious gastric residual. All oral feedings were stopped. He continued to receive TPN and underwent abdominal decompression for necrotizing enterocolitis. Oral feedings were restarted on Day of Life 28. On discharge, the infant's weight was 2,230 g, length was 43.5 cm, and head circumference was 30.5 cm; these measurements were at the 5th, 2nd, and 3rd percentiles, respectively, on the Fenton Growth chart. This infant experienced growth failure in the preterm infant.

This model case contains every attribute for growth failure in preterm infants during initial hospitalization in the NICU. This preterm infant experienced insufficient nutritional support, including delayed feedings. He also experienced excessive energy expenditure related to secondary infection (necrotizing enterocolitis) that resulted in temperature instability and feeding intolerance. Finally, his weight at discharge from the NICU was less than the 10th percentile on a standardized preterm infant growth chart, which indicated suboptimal physiologic growth.

Contrary Case

A preterm male infant was born at 32 0/7 weeks gestation. At birth, his weight was 1,680 g, length was 40.5 cm, and head circumference was 28.5 cm; these measurements were at the 38th, 28th , and 27th percentiles, respectively, on the Fenton Growth chart. At birth he required continuous positive airway pressure for respiratory support. A solution of 5% dextrose in water was immediately started on an intravenous umbilical line. Total parenteral nutrition with 10% amino acids, 10% dextrose, and 20% lipids was started at 4 hours of life. Within the first 6 hours of life, the first enteral feeding of colostrum was administered. His mother was able to provide skin-to-skin kangaroo care on Day of Life 1 and daily throughout the NICU stay. His mother worked very closely with NICU staff to provide maternal milk feedings every 3 to 4 hours enterally. On Day of Life 3, continuous positive airway pressure was removed, and he was able to

breathe without respiratory support. On Day of Life 4, TPN and parental nutrition were discontinued. He showed no evidence of infection throughout the NICU stay. On Day of Life 21, enteral feedings were ended, and he was able to take all feedings from bottle and/or breast. He was discharged on Day of Life 35. At discharge, his weight was 2,475 g, length was 46 cm, and head circumference was 31.5 cm; these measurements were at the 14th, 17th, and 11th percentiles on the Fenton Growth chart. This preterm male infant did not experience growth failure.

Antecedents and Consequences

Antecedents

Two antecedents of growth failure in preterm infants were identified: preterm human infant birth and gestational viability. A *preterm infant* is defined as an underdeveloped human infant born before 37 completed weeks of gestation (World Health Organization, 2016). Gestational viability is defined as greater than 23 weeks gestational age and/or greater than 400-g birth weight (Zaichkin & Weiner, 2011). The antecedents of growth failure in preterm infants are summarized in Figure 1.

Consequences

In the case of growth failure in preterm infants, three consequences were identified: increased length of NICU stay, poor neurodevelopmental and health outcomes, and poor long-term growth. The consequences of growth failure in preterm infants are summarized in Figure 1.

Increased length of NICU stay. The length of NICU stay is increased when a preterm infant experiences growth failure. Generally, the earlier in the gestation that an infant is born, the longer the stay in the NICU (Gilbert, Nesbitt, & Danielsen, 2003). Growth failure in preterm infants is associated with health problems, including physiologic instability, poor suck-swallow-breathe coordination, impaired swallowing, and poor oral motor control (Barlow, 2009). Until a preterm infant can maintain physiologic stability, effective oral feeding, consistent weight gain, and good oral motor control, she or he will remain in the NICU.

Poor neurodevelopmental and health outcomes. Growth failure in preterm infants has consequences for short- and long-term health. In humans, brain growth is most rapid in the time immediately before and after birth (Embleton & Tinnion, 2009). In the time between 24 weeks gestation and 2 years after birth, the brain reaches 90% of its final volume (Embleton & Tinnion, 2009). Growth failure in preterm infants that occurs during this postnatal period also can cause suboptimal brain growth and consequent irreversible neurodevelopmental deficits, including abnormal motor and cognitive function (Butler et al., 2013; Embleton & Tinnion, 2009; Pfister & Ramel, 2014). Growth failure in preterm infants and subsequent infant catch-up growth is related to other adverse health outcomes, including decreased insulin sensitivity, increased insulin resistance, altered adipose tissue metabolism (Finken et al., 2006), and increased adverse cardiovascular changes such as hypertension (Thomas et al., 2011).

Growth failure of preterm infants is more than inadequate weight gain and must be managed to prevent increased risk for morbidities during future development.

Poor long-term growth. Growth failure in preterm infants is a predictor for poor long-term growth. Throughout childhood, children who were preterm infants with histories of growth failure were smaller than age-matched control infants (Westerberg et al., 2010). Despite predisposition for accelerated growth, many preterm infants do not experience catch-up growth (Claas et al., 2011). Claas et al. (2011) found that catch-up growth did not occur by 5.5 years of age in 71.4% (weight), 44.8% (height), and 31.1% (head circumference) of preterm infants who experienced preterm infant growth failure.

Empirical Referents

Because the concept of growth failure in preterm infants is not abstract, the empirical referents are identical to the defining attributes. A standardized preterm infant growth chart may be considered an empirical referent that aids in measurement of a defining attribute, suboptimal physiologic growth. However, this measurement tool offers only partial conceptual fidelity because weight is only the sum of the mass as a single measurement that does not address nutritional, biological, or environmental conditions (Bertino, Milani, Fabris, & De Curtis, 2007).

Proposed Operational Definition

Based on the current state of the science, we propose that *growth failure in the preterm infant in*

the NICU be defined as suboptimal growth with weight at less than the 10th percentile for post-menstrual age on a standardized preterm infant growth chart at discharge from the NICU caused by excessive energy expenditure and insufficient nutritional support.

Conclusion

Growth failure of preterm infants is more than inadequate weight gain and must be managed to prevent increased risk for morbidities during future development. Growth failure in preterm infants in the NICU is a multifaceted concept, as shown in the diversity of the literature and concept analyses. In this conceptual analysis, we examined the fundamental elements, clarified the meaning, and developed an operational definition of growth failure in preterm infants. The proposed operational definition of *growth failure in the preterm infant in the NICU* will promote a unified use of the concept in theoretical construction, research, and clinical practice. Further research is needed to determine if a goal growth velocity should continue to be based on a reference fetus. If members of the research, nursing, medicine, and nutrition science communities are familiar with the key attributes of growth failure in preterm infants, they will be better able to promote optimal preterm infant growth and limit adverse outcomes of insufficient preterm infant growth during the NICU hospitalization.

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Chapter III: Review of the Literature

Many questions remain unanswered or unclear surrounding preterm infant growth and nutrition, including: What is appropriate growth? How should growth be measured? Are our current measurement tools of growth reliable? Should preterm nutrition be fortified or lactoengineered? What are the optimal nutritional practices to produce optimal growth? How should nutrition be delivered? The purpose of this chapter is to review the literature on preterm infant growth and nutrition management to examine the current state of the science and to identify the gap in literature for questions such as these. This review of literature is organized by seven sections: appropriate preterm infant growth, current measures of growth, body composition, delivery of nutrition in the NICU, types of nutrition, fortification of human milk, and cost of human milk in the NICU. By examining the current literature, the gaps in knowledge related to preterm infant nutrition and growth can be discovered and recommendations for future research can be made.

Appropriate Preterm Infant Growth

In this section, I will review the importance of appropriate preterm infant growth and the subsequent consequences that occur when preterm infants experience growth failure and/or catch-up growth.

Most health care providers guided by the AAP strive to prescribe nutritional practices in the NICU to achieve growth and body composition comparable to intrauterine life (Hay, 2013; Kleinman & American Academy of Pediatrics, 2009; Puntis, 2006). Intrauterine growth is commonly used as the standard for extrauterine growth of preterm infants because a superior growth standard remains undefined (Fenton & Kim, 2013). The recommended growth standard based on intrauterine growth is 15 gm/kg/day (Poindexter, 2014). If this growth standard was an

appropriate goal, the challenge still exists that there are not existent guidelines on how to achieve this fetal growth rate, as the actual nutrients delivered in utero are unknown (Sauer, 2007). However, there is lack of evidence to demonstrate that it is optimal or safe to set the goal of extrauterine growth of preterm infants to mimic intrauterine growth (Pereira-da-Silva & Virella, 2014). The recommended growth standard is controversial, because the reference fetus used to develop this standard was based on a small data set and was not gender specific. Intrauterine growth commonly reflects an ideal growth pattern that is rarely achieved in hospitalized preterm infants (Horemuzova, Söder, & Hagenäs, 2012). Based on applying intrauterine growth standards, hospitalized preterm infants frequently experience growth failure (Martin et al., 2009).

Preterm infant growth failure is frequently defined as weight less than the 10th percentile for postmenstrual age on a standardized growth chart at discharge from the NICU (Martin et al., 2009; McLeod & Sherriff, 2007; Ruth, 2008). Approximately 90% of very low birth weight (VLBW) infants are classified as having experienced growth failure by 36 weeks corrected gestational age (Dusick et al., 2003). Growth failure in preterm infants is associated with growth velocity rates less than 15 gm/kg/day in weight, 0.5 to 0.7 cm/week in head circumference, and/or 1 cm/week in length (Greer & Olsen, 2013; Griffin, 2017). Growth velocity is calculated as increase in grams per kilogram per day (Greer & Olsen, 2013; Patel, Engstrom, Meier, Jegier, & Kimura, 2009) and increase in centimeters per week in head circumference and length (Greer & Olsen, 2013).

Weight gain at the recommended growth velocity of 15 gm/kg/day can still result in failure to return to birth weight percentile when plotted on a standard preterm infant growth chart (Martin et al., 2009; Reali et al., 2015; Ruth, 2008). Martin et al. (2009) reported that even when the study infants exceeded the growth velocity of 15 gm/kg/day, growth failure occurred in 75%

of the 1,187 infants studied. Reali et al. (2015) reported that despite an average growth velocity of 16.04 gm/kg/day in preterm infants during their hospitalizations, 72.3% weighed less than the 10th percentile on a standard preterm infant growth chart at discharge from the hospital.

There are multiple reasons for postnatal preterm infant growth failure. While we commonly consider nutrition as the cause of growth failure in preterm infants, conditions including genetic-acquired diseases, liver disease, endocrine abnormalities, surgery, infections, sepsis, ventilator dependence, respiratory distress, persistent pulmonary dysfunction, hypothermia, cold stress, and postnatal exposure to dexamethasone are also contributing factors (Bartholomew et al., 2013; Hay, Brown & Denne, 2014; Vinall et al., 2012). The drugs used to treat biological conditions prenatal in mother and fetus and postnatal in the infant can also negatively affect infant nutrient metabolism and growth (Hay, 2013).

Consequences of Growth Failure

Preterm infant growth failure is associated with adverse neurodevelopmental outcomes, decreased somatic development, longer NICU stay, and potentially preventable morbidities (McLeod & Sherriff, 2007; Vasu & Modi, 2007; Walker et al., 2014). In humans, brain growth is most rapid in the time immediately before and after birth (Embleton & Tinnion, 2009). In the time between 24 weeks gestation and two years after birth, the brain reaches 90% of its final volume (Embleton & Tinnion, 2009). Malnutrition and subsequent growth failure in preterm infants that occurs during this postnatal period can impact both the function and structure of the brain and development of the retina (Uauy & Mena, 2001). Impeded brain growth can result in irreversible neurodevelopmental deficits, including abnormal motor and cognitive function (Butler et al., 2013; Embleton & Tinnion, 2009; McLeod & Sherriff, 2007; Walker et al., 2014).

Consequences of Catch-Up Growth

Catch-up growth is defined as length and weight gain greater than intrauterine growth rate for gestational age during a preterm infant's first weeks of life (Roggero et al., 2009; Sauer, 2007). There appear to be benefits and consequences of catch-up growth. While some researchers suggest that catch-up growth is required for preterm infant brain development, others report that it places the infant at increased risk of harmful cardiovascular and metabolic outcomes later in life (Kiger, Taylor, Wagner, Finch, & Katikaneni, 2016; McLeod et al., 2015; Ong, Ahmed , Emmett, Preece, & Dunger, 2000; Sauer, 2007).

The concern of rapid catch-up growth is based on the concept of Barker's hypothesis, which demonstrates a relationship between fetal and neonatal growth, and alteration of subsequent metabolic and cardiac function (Hales & Barker, 1992). Hales & Barker (1992) hypothesized that low birth weight infants undergo fetal programming, which causes physiological adaptations in response to the intrauterine environment to increase likelihood of postnatal survival. It is not clear whether the growth and fat deposition itself is harmful or whether the growth is related to nutritional adaptations and metabolic programming that increase risk for later disease (Wells, 2012).

Preterm infants commonly display intra-abdominal adiposity and abnormal body composition during catch-up growth (Strydom, Van Niekerk & Dhansay, 2017). Rapid accretion of adipose tissue may cause adverse neonatal programming that can include changes in organ structure and function, including muscle mass, beta cell mass, and nephron number, which contributes to metabolic capacity (Wells, 2012). Muhlhausler et al. (2009) reported that rapid catch-up growth was associated with upregulation of IGF1 receptors and insulin, which is mediated by nutritional intake that can contribute to later metabolic risk. Deposition of visceral

intra-abdominal fat in preterm infants may increase risk for disease in adulthood, including increased insulin resistance, decreased insulin sensitivity, type II diabetes, altered adipose tissue metabolism, metabolic syndrome, cerebrovascular accident, cardiovascular disease, and obesity (Barker, 1997; Barker, Eriksson, Forsen, & Osmond 2002; Embleton et al., 2017; Finken et al., 2006; Strydom et al., 2017; Thomas et al., 2011; Yeung, 2006). Metabolic capacity is strongly correlated with chronic disease risk (Wells, 2012). These changes to organ structure and function are strongly dependent on fetal and early infant growth (Wells, 2012).

Rapid catch-up growth appears to pose most risk during the first few weeks of life (Stettler et al., 2005). Some researchers suggest that high birth weight may index metabolic programming over the lifespan (Barker, 1997, Wells, 2012). In contrast, other researchers argue that it is the change in size of the infant and not birth weight, which is the primary factor that contributes to increased metabolic and cardiac disease risk (Singhal & Lucas, 2004). In a longitudinal study, rapid body mass index (BMI) gain in preterm infants at calendar age four, 12, and 18 months was associated with higher odds of being overweight or obese at eight and 18 years of age (Belfort, Gillman, Buka, Casey, & McCormick, 2013).

There is not a clear understanding by researchers and clinicians of the consequences of too rapid growth. The current literature on preterm infant catch-up growth and subsequent increased body fat suggests that the current growth and nutrition recommendations are not effective or safe to achieve normalized body composition postnatally. Breastfeeding has been shown to promote slower growth, while artificial feeding may stimulate higher growth velocity postnatally (Oddy, 2012). Human milk can induce lower plasma insulin levels resulting in decreased fat storage, preventing excessive development of adipocytes resulting in a protective effect on obesity (Oddy, 2012). It is possible that lower nutrient intake and slower growth may

be protective longitudinally for preterm infants (Embleton et al., 2017). Future research is needed to examine the relationship between fetal and neonatal growth and alteration of subsequent metabolic and cardiac function to prevent risk for harm later in life.

Current Measures of Growth

In this section, I review the current measures of growth most frequently utilized in the NICU. I will begin by examining how the literature defines and describes growth. Second, I will describe anthropometric measures and growth charts, including the reliability and utility of these measures. Accurately obtained anthropometric measures serve as the current best practice in the NICU to measure growth and manage growth issues (Greer & Olsen, 2013).

Growth is described as an increase in size of tissue because of increase in intracellular substance or multiplication of cells (Shrestha, 2017). Preterm infant growth requires constant evaluation as it is used to inform daily nutritional practices in the NICU (Greer & Olsen, 2013). Both quantitative and quality measures of preterm infant growth are important to identify and describe target growth rates. Quantitative measures include anthropometric and body composition measures. Quality measures include body composition measures.

Anthropometric Measures

The most common anthropometric measurements obtained on preterm infants in the NICU include weight, length, and head circumference (Anderson, 2014). The frequency of these measures should include accurate weights obtained daily and length and head circumference measurements obtained weekly (Anderson, 2014; Greer & Olsen, 2013; Poindexter, 2014). These measures should be plotted on a standardized growth chart at the same time each week during the NICU stay (Anderson, 2014, Greer & Olsen, 2013; McLeod & Sherriff, 2007). The data obtained from the anthropometric measures should then be used to calculate growth velocity

(Greer & Olsen, 2013). Growth velocity is calculated in gm/kg/day and cm/week (Greer & Olsen, 2013).

The reliability of these anthropometric growth measures has been questioned. It is important to determine the reliability of obtaining anthropometric measures, as inaccurate neonatal measurements can contribute to inappropriate nutritional management and failure to detect growth failure (Wood, Raynes-Greenow, Carberry, & Jeffery, 2013). Emphasis is commonly placed on accurate weight measures when evaluating nutritional practices, which can result in viewing length and head circumference as secondary measures. As a result, the importance of reliability and accuracy of length and head circumference are often overlooked in clinical practice (Wood et al., 2013). In examination of preterm infant growth studies, it is vital to comprehend the reliability of these anthropometric measures, as they are a direct indicator of the quality of data.

While head circumference measures are an important reflection of brain growth, the precision and accuracy in obtaining correct measures is lacking (Embleton et al., 2017). Bhushan and Paneth (1991) reported 5% of the head circumference measures in 1,105 infants weighing less than 2,000 grams differed by 2 cm or greater. Sutter, Engstrom, Johnson, Kavanaugh, and Ifft (1997) reported that head circumference measures of preterm infants using a paper tape was more reliable than use of cloth tape measures.

Multiple techniques are available to measure infant lengths. Length-board measures obtained by trained professionals have been reported as being the most reliable (Johnson, Engstrom, Warda, Kabat, & Peters, 1998; Corkins, Lewis, Cruse, Gupta, & Fitzgerald, 2002). Corkins et al. (2002) reported an average difference of 2.23 cm between tape measure measures and length board measures; while this was not statistically significant, it was clinically

significant. The difference in these measures resulted in 13 of 25 patients having a change in weight for length percentile (Corkins et al., 2002). Johnson et al. (1998) reported that crown-heel technique was the least reliable length measurement method in full term infants. Length board is accepted as the standard for obtaining length measures with reproducible accuracy within 0.2 cm to 0.4 cm (Feucht, 2000).

The reliability of weight measurements is influenced by multiple factors, including method of reading and recording weights, number of individuals performing the measures, balance of scale, technique, constancy of infant conditions, and type of scale (Kavanaugh, Meier, & Engstrom, 1989). Kavanaugh, Engstrom, Meier, and Lysakowski (1990) reported that type of scale may be the most crucial control for reliability. Kavanaugh et al. (1990) examined weight in 50 preterm infants and reported that an electronic scale was more reliable than the mechanical scale. The mean difference for intrarater measures was 5.5 grams (mechanical scale) and 1.36 grams (electronic scale, Kavanaugh et al., 1990). The percent of interrater difference more than 5 grams was 0% for electronic scale and 66% for mechanical scale (Kavanaugh et al., 1990). Kavanaugh et al. (1989) reported that mechanical scales do not have the sufficient reliability for use in research.

While the current available literature discussed reviewing reliability of weight, length, and head circumference techniques are dated, they serve as landmark studies. The measurement devices have not made significant technological advances since the time these research studies were published. The gap in literature examining the reliability of anthropometric measures within the preterm infant population exists because there are very few growth studies that provide detailed measurement reliability assessments and description of anthropometric standardization (Onis, 2006).

Other anthropometric indices, including ponderal index (weight/length^3), body mass index (BMI or weight/length^2), body surface area, Benn index, and weight to length ratio, may be useful to examine body proportionality as a proxy for body composition (Greer & Olson, 2013; Kiger et al., 2016). However, these methods have not been validated to estimate preterm infant body composition (Kiger et al., 2016). Kiger et al. (2016) reported that when anthropometric measures were examined that BMI most closely predicted percentage body fat. Body mass index only had a low predictive value for body fat, with a predictive power of 51% in infants less than 50 weeks post menstrual age and 16% in infants greater or equal to 50 weeks post menstrual age. Further research is needed to validate these anthropometric indices to examine body proportionality as a proxy for body composition in preterm infants.

Growth Charts

Clinicians use growth charts in the NICU to document a visual display of growth over time. Growth measures plotted on growth charts are utilized to make daily informed recommendations on preterm infant feeding (Greer & Olsen, 2013). Although multiple growth charts have been developed to monitor infant growth, the two primary types of growth charts in the NICU are growth standard charts and growth reference charts. The selection of growth charts used in NICUs depends on local practice and provider preference (Griffin, 2017).

Growth reference charts are descriptive and represent how a population is growing (Villar et al., 2010). Growth reference charts are created based on statistical summary of anthropometric measurements of a reference group (Villar et al., 2010). Growth reference charts include fetal estimation curves, birth weight for gestational age charts, and postnatal longitudinal growth charts (Villar et al., 2010). Fetal estimation curves are based on fetal ultrasound anthropometric measurements across multiple gestational ages. Birth weight for gestational age charts represent

actual growth of infants constructed from a single anthropometric measure of weight obtained at birth across multiple different gestational ages. Postnatal longitudinal growth charts represent actual postnatal growth from a reference group over time. Growth reference charts describe anthropometry of the population, but they do not account for environmental, nutritional, socioeconomic, and health conditions (Bertino, Milani, Fabris, & De Curtis, 2007).

In contrast, growth standard charts define how a population should be growing under optimal nutritional and environmental conditions, as opposed to how they have grown during a specific time and place (Giuliani et al., 2016; Villar et al., 2010). Growth standard charts represent longitudinal monitoring of prospective healthy growth (Villar et al., 2010). However, growth standard charts do not inform preterm infant growth assessments until infants reach postmenstrual age equal or greater to 37 weeks (Fenton & Kim, 2013). Postmenstrual age is defined as gestational age plus chronological age post-birth (Engle, 2004).

The 2013 Fenton Preterm Growth Chart, a growth reference chart, is one of the most widely used growth charts to monitor preterm infant growth in the NICU (Fenton & Kim, 2013). This growth chart combines fetal growth patterns based on weight for gestational age for preterm infants combined with the World Health Organization (WHO) growth standards of term infants (Fenton & Kim, 2013). The strength of the 2013 Fenton Preterm Growth Chart is that it provides a single tool that assesses how the infant grew while in the uterus based on birth weight and then is used to monitor postnatal growth to and beyond term (Pereira-da-Silva & Virella, 2014).

Major revisions of preterm infant growth charts have been made over the past 5 to 10 years in efforts to recognize the importance of nutrition and growth and in an attempt to quantify preterm infant growth (Kiger et al., 2016). The growth charts available serve well to statistically

describe anthropometric measures of growth; however, there is no causal relationship between these measures and estimation of actual body composition (Kiger et al., 2016).

Body Composition

In this following section, I review how quality of growth is measured quantitatively by measuring body composition. There are multiple methods currently available to assess preterm infant body composition. The methods used to examine preterm infant body composition will be described as compartment models (see Figure 2). Furthermore, the different compartment models fit into three broadly categorized methods and are described as: gold standard methods, reference methods, and predictive methods. Lastly, I examine the differences and similarities between preterm infant and term infant body composition.

Weight is described as the sum of the mass (Johnson, 2003). Some researchers have argued that weight gain by itself is not adequate to inform the practice of nutrition on growth (Forsum, Olhager, & Tornqvist, 2016). It has been suggested that instead, body composition should be measured as a parameter of growth to inform nutritional practices (Forsum et al., 2016). This is a paradigm shift from focusing on the quantity of growth to the quality of growth in preterm infants. Body composition of preterm infants is widely variable (Kiger et al., 2016). Understanding the composition of growth is vital, as it may be predictive of future disease risk (Wells, 2012).

Compartment Methods

The methods discussed within this paper used to measure preterm infant body composition include two-, three-, and four-compartment models. These methods examine body composition by dividing body weight into compartments that contain distinctive components (Ellis, 2007; Strydom et al., 2017). Each compartment method is built upon the previous method.

The earliest and most frequently used model is a two-compartment model (Ellis, 2000). The two-compartment model examines body composition in two components: fat free mass (FFM) and fat mass (FM; Ellis, 2000; Wells, 2012). Fat free mass includes internal organs, muscle, bone, water, and connective tissue. Fat mass includes adipose tissue and fat (Strydom et al., 2017). The three-component model measures FM and divides FFM into two parts: water and any remaining solids (Ellis, 2000). A limitation of the three-compartment model is that if the body protein and/or bone mineral mass is depleted, the density of solids is inaccurate (Ellis, 2000). Thus, the four-compartment model was created and measures FM and divides FFM into three physiological compartments: body cell mass, extracellular water, and extracellular solids (Ellis, 2000).

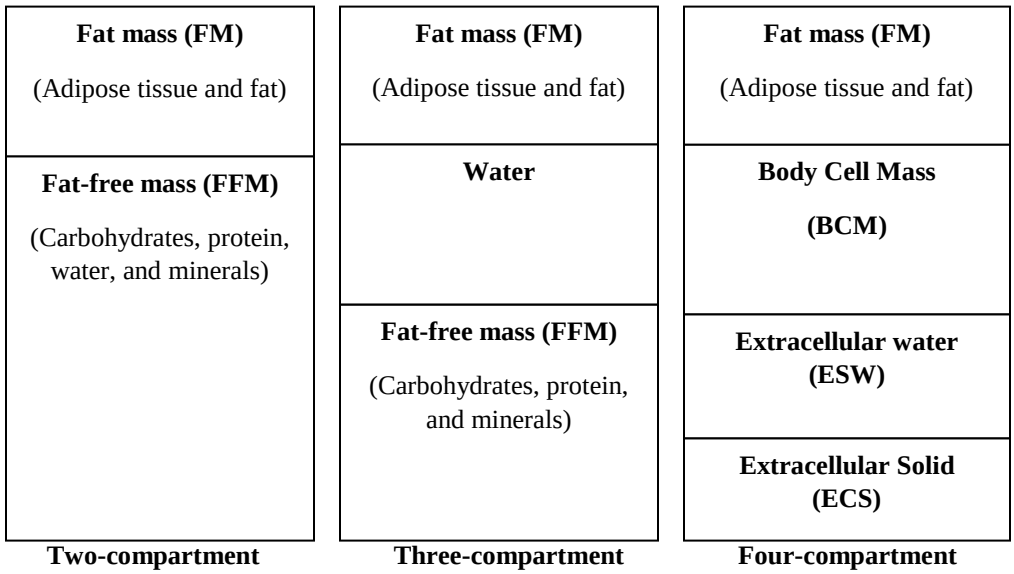

Figure 2. Different models of body composition used for infants (adapted from Ellis, 2007, and Strydom et al., 2017).

Gold Standard Methods

Magnetic resonance imaging (MRI). Magnetic resonance imaging uses strong magnetic field to align water molecules that contain hydrogen nuclei (Ellis, 2000). The intensity of the signal can measure the number of hydrogen nuclei in the body tissue (Ellis, 2000). This process provides detailed visual cross-sectional images of the body and can measures total body fat,

abdominal fat, visceral fat, subcutaneous fat, and ectopic fat (Ellis, 2000; Wells, 2012). There are limitations in use of MRI for preterm infant body composition assessment. Magnetic resonance imaging scanning is costly, requires special facilities and specialized computer software for infants, requires removal of the infant from the NICU, and necessitates the infant to be still for accurate results (Wells, 2012). There is also a high demand of MRI for clinical diagnostic use, which limits availability for use of body composition assessment (Ellis, 2007).

Reference Methods

Dual-energy x-ray absorptiometry (DXA). Dual-energy X-ray absorptiometry utilizes, Low intensity collimated X-ray beams at two energies to scan the whole body or at specific bone sites, such as the hip and spine…. For a whole body scan, values for body fat and non-fat soft tissue mass are obtained. (Ellis, 2007, p. 89).

There are limitations of use of DXA in preterm infants. Dual-energy x-ray absorptiometry is expensive, requires the infant to be removed from the NICU, and requires the infant to be still for accurate results (Ellis, 2007). There are also concerns over low level radiation that is used in DXA during the sensitive developmental window in preterm infants (Wells, 2012).

Isotope dilution. Isotope dilution utilizes a tracer administered orally or intravenously, and the volume of a compartment can be defined as the ratio of the dose of this tracer to its concentration in that body compartment (Ellis, 2000). Generally, a fluid sample of blood, urine, or saliva is obtained prior to administration of the isotope tracer for baseline and then a second sample is obtained after waiting the appropriate amount of time for the tracer to penetrate the compartment of interest (Ellis, 2000). Isotope dilution has been successful after six weeks of birth in providing data on FFM and FM (Chomtho, Wells, Davies, Lucas, & Fewtrell, 2009).

There are limitations to use of isotope dilution in the neonatal population. It can be difficult to obtain appropriate saliva samples or urine sample, and a part of the isotope dosing can be unsuccessful due to spilling/incomplete feeding (Wells, 2012). Isotope dilution is limited in the first six weeks after birth, as urine output volume is smaller. Isotope dilution analysis requires mass spectrometry or spectrophotometry, which is expensive and time consuming (Wells, 2012). In addition, repeat measurements should only be conducted when the tracer from the previous measurement has cleared the body, which is typically 10 to 14 days in infants (Ellis, 2007). The limitation of frequency of measurements is a clear disadvantage.

Air displacement plethysmography. Air displacement plethysmography (ADP) calculates proportion body fat from body weight and volume by measuring bone density (Forsum et al., 2016; Wells, 2012). Air displacement plethysmography provides a direct measurement of body fat percentage (Kiger et al, 2016). Air displacement plethysmography for infants was introduced in 2004 as the PEA POD (Forsum et al., 2016; Wells, 2012). The PEA POD can accommodate infants from 1 kg to 8 kg and can tolerate moderate levels of infant activity (Wells, 2012). Air displacement plethysmography provides instantaneous results, is well tolerated by infants, portable, and a noninvasive method that is ideal for serial measures to determine body composition (McLeod et al., 2015; Roggero et al., 2012).

The accuracy and reliability of ADP to determine body composition in preterm infants is argued among researchers. Air displacement plethysmography compared to DXA measurements was found to have a strong correlation between methods to determine body composition in preterm infants (Fields, Demerath, Pietrobelli, & Chandler-Laney, 2012). Direct confirmation of ADP to accurately predict fat was found by examining live piglets with comparable weight of VLBW infants and comparing them post mortem (Frondas-Chauty, Louveau, Le Huerou-Luron,

Roze, & Darmaun, 2012). Air displacement plethysmography was sensitive in assessing the preterm infant's macronutrient and total energy intake on changes in body composition as early as 31 weeks corrected gestational age (McLeod et al., 2015).

Roggero et al. (2012) examined preterm infant body composition comparing ADP with reference H(2) 18O dilution method in 79 preterm infants and found ADP was accurate to determine FM and interdevice reliability was strong (regression analysis, $p < 0.001$). Roggero et al. (2012) used a two-component model based on total body water in order to calculate reference estimates of body composition. It has been argued that a two-component model is not adequate to examine body composition, as information regarding hydration and density of fat-free mass is incomplete, and a three- or four-component model should be used (International Atomic Energy Agency, 2009; Mcleod et al., 2015).

Forsum et al. (2016) performed the first validation study using a three-compartment model in moderately preterm infants during the first week of life using the PEA POD to provide estimates of FFM density and FM. The study found that individual estimates of FM may have deviated significantly from the reference values and that FFM density values were biased; however, the average estimates of FM were satisfactory (Forsum et al., 2016). Based on these findings, the researchers argued that the PEA POD has not been appropriately validated to determine body composition in preterm infants and requires further studies on the accuracy of the PEA POD system (Forsum et al., 2016; McLeod et al., 2015).

There are other limitations in using ADP in the neonatal population. Air displacement plethysmography is not widely available in NICUs (Kiger et al., 2016). Commonly cited reasons ADP is not widely used in NICUs include medically instability, specialty calibrations for all

equipment for each single infant use, convenience, cost, and personal preference of traditional anthropometric methods (Kiger et al., 2016).

Predictive Measures

Bio-electrical impedance. Bio-electrical impedance (BIA) is a method to assess body composition through measuring resistance or impedance of the body (Strydom et al., 2017). Bio-electrical impedance is performed by sending a weak alternating current at a fixed frequency through the infant's body (Collins et al., 2013). According to Strydom et al. (2017),

> The measure of impedance is directly and inversely proportional to the volume of conductor through which the current flows. In the human body the conductor is the total body water (TBW), as it is almost entirely found in lean body mass (LBM). (p. 4)

As a result, FFM can be estimated by converting the measured resistance and used with the two-compartment model to estimate FM (Ellis, 2007). Fat mass and bone are resistant to bio-electrical impedance (Strydom et al., 2017). Bio-electrical impedance is inexpensive, simple, quick, safe, and minimally invasive, and measurements can be made frequently and can be completed at the bedside of a preterm infant without removal of respiratory support or monitoring cords (Collins et al., 2013, Lingwood et al., 2012).

There are limitations for the use of BIA in the neonatal population. Wells (2012) suggested that BIA is not appropriate in the neonatal population as is requires muscles to be in a relaxed state, which is difficult to accomplish without sedation. Dung, Fusch, Armbrust, Jochum, and Fusch (2007) reported that there is no clear evidence confirming the use of FFM prediction equations in preterm neonates utilizing BIA. Raghavan et al. (1998) and Ellis (2000) found that BIA did not have significant advantage over basic anthropometric length and weight measures in infants.

Skinfold thickness. Skinfold thickness measurements are obtained using caliper measurements to determine neonatal local subcutaneous fat distribution and evaluate distribution of FM in body regions (Strydom et al., 2017; Wells, 2012). Skinfold thickness measurements are simple and an inexpensive method to determine body composition that can be performed at the bedside (Simsek et al., 2015; Demerath & Fields, 2014).

There are limitations to use of in the neonatal population. Limitations include possible invasiveness related to size of instruments compared to infant and possibly injuring the skin and causing pain, specifically in extremely low birth weight (ELBW) infants with immature friable skin (Strydom et al., 2017). Skinfold thickness measurements are significantly influenced by the infant's hydration status (Strydom et al., 2017). A preterm infant's hydration status is not constant, and sick infants can have extreme fluctuations in body water (Ellis, 2007; Strydom et al., 2017; Ellis, 2007). Any body composition results obtained using indirect or direct measures of body water with a two-compartment model should be done cautiously (Strydom et al., 2017). Lastly, it is unknown whether the data obtained from skin fold thickness accurately informs whole body fat measurements or total lean tissue in preterm infants (Wells, 2012).

Due to the concerns regarding the ability of skinfold thickness measures to accurately inform whole body fat measures, an advanced method of combining skinfold thickness at two primary sites and nine body dimensions, Dauncey anthropometric model, was developed. The Dauncey anthropometric model uses skinfold thickness subscapular and triceps measurements; circumference of the head, chest, abdomen at the umbilicus, mid-upper arm, mid-thigh, and mid-calf; and lengths of the upper arm, lower arm, and crown-rump length (Dauncey, Gandy, & Gairdner, 1977). The Dauncey anthropometric model has been considered one of the best

methods to accurately determine body composition, specifically in resource poor countries (Strydom et al., 2017).

Preterm versus Term Infant Body Composition

In a systematic review and meta-analysis examining body composition of preterm infants at term equivalent age (TEA) compared to full term infants, TEA infants had greater percentage total body fat, which was explained by lesser lean tissue rather than increase in FM (Johnson et al., 2012). Preterm infants at TEA have similar FM to term infants. Preterm infants at TEA were lighter, shorter, with a smaller head circumference compared to full term infants (Johnson et al., 2012). Similarly, Gianni et al. (2016) examined body composition using ADP in late preterm infants according to percentile at birth on day of life five and at term. Gianni et al. (2016) reported that at birth, the preterm infant group had lower FM and FFM compared to term infants. During the study, the FM and FFM increased significantly in the preterm infant group (Chi-squared, $p < 0.00001$). At term, the FM index was significantly higher, but not FFM, in late preterm infants compared to term reference infants (Chi-squared, $p < 0.00001$; Gianni et al., 2016). As a result of more FM and less FFM, a higher total fat percentage occurs (Strydom et al., 2017).

Delivery of Nutrition in the NICU

In this section, I will review how nutrition is delivered in the NICU. Nutrition management in preterm infants can include parental nutrition, enteral nutrition, and/or oral nutrition based on clinical condition and gestational age (Anderson, 2014). Lastly, I will briefly explore demand feedings and the importance of frequency of feedings.

Parental Nutrition

Parental nutrition provides nutrients intravenously and is standard of care for most extremely preterm infants during first days of life (Anderson, 2014; Embleton & Simmer, 2014). Parental nutrition is used to treat preterm infants that cannot be fed orally or enterally (Anderson, 2014; Koletzko, Goulet, Hunt, Krohn, & Shamir, 2005). Parental nutrition can provide glucose, electrolytes, amino acids, and lipids (Embleton & Simmer, 2014). There is consensus that extremely preterm infants or those weighing < 1,500 gram will benefit from parental nutrition (Embleton & Simmer, 2014). It is unclear if days of life, weight gain, gestational age, and/or physiologic stability, individually or in combination, are the optimal indicators to stop parental nutrition (Embleton & Simmer, 2014). Many practitioners recommend parental nutrition in preterm infants born < 32 weeks, weighing < 1,500 grams, and in more mature preterm infants until full enteral feedings are established (Embleton & Simmer, 2014). Parental nutrition commonly serves as an adjunct and bridge to enteral nutrition in preterm infants (Dutta et al., 2015).

Parental nutrition should be started as soon as possible after birth on day of life one (Embleton & Simmer, 2014). Despite this practice guideline, in a systematic review of literature Lapillonne and Kermorvant-Duchemin (2013) reported that parental nutrition was only initiated day of birth in 24% to 54% of respondents and 67% to 94% of respondents on day of life two. There is a need for continued education among neonatal providers to reach compliance with current practice guidelines.

Standardized parental nutrition is commonly initiated at birth and then individualized on day of life two (Embleton & Simmer, 2014). Parental nutrition should be decreased as enteral milk volumes are increased, and should not exceed total fluid intake of 15 – 175 mg/kg/day

during the first few days of life (Embleton & Simmer, 2014). Parental nutrition should be stopped once the preterm infant is tolerating enteral volumes of 125 – 150 ml/kg/day (Embleton & Simmer, 2014). Bridging from parental nutrition to full enteral feeding is typically achieved in one to two weeks and closely correlates with degree of prematurity (Embleton, Pang, & Cooke, 2001).

Enteral Nutrition

Enteral feedings provides nutrition directly into the gastrointestinal (GI) system via nasogastric or orogastric tube (Anderson, 2014). Enteral nutrition is preferred to parental nutrition, as it avoids complications secondary to vascular catheterization, sepsis, fasting, and adverse effects of parental nutrition (Dutta et al., 2015). A primary nutritional goal when feeding preterm infants is to reach full enteral feedings in the shortest time, while simultaneously maintaining optimal growth and avoiding adverse effects of rapid feeding advancement (Senterre, 2014). How to reach this goal is highly controversial.

Fresh mother's milk is the preferable choice to begin enteral nutrition, followed by frozen mother's milk, pasteurized donor human milk, and preterm formula, respectively (Dutta et al., 2015). It is acceptable to wait 24 to 48 hours for mother's milk or PDHM to be available to start minimal enteral feedings (Dutta et al., 2015). If mother's milk or PDHM is not available at 48 hours, formula can be considered (Dutta et al., 2015).

Enteral nutrition should be initiated in ELBW and VLBW infants between six and 48 hours of life (Senterre, 2014), preferably within 24 hours of life (Dutta et al., 2015; Embleton et al., 2017). Priming the GI system with colostrum is important to prevent GI mucosal dysfunction and atrophy (Neu, 2007). In the NICU, enteral feedings are usually started as minimal enteral feedings. Minimal enteral or trophic feedings are small feedings less or equal to 24 ml/kg/day to

prime the gut and promote maturation of the GI system (Dutta et al., 2015; Neu, 2007). In a systematic review, Morgan, Bombell, and McGuire (2013) found that early introduction of enteral nutrition compared to fasting in VLBW infants correlated with reaching full feedings earlier (mean difference − 1.05 days [95% CI −2.61, 0.51]).

Advancement of enteral nutrition should be individualized based on preterm infant body weight and clinical condition (Senterre, 2014). A reasonable approach to advancing enteral nutrition is by starting at 20 – 30 ml/kg/day in VLBW infants and increase by 30 ml/kg/day and start at 15 – 25 ml/kg/day in ELBW infants and increase by 15 – 20 ml/kg/day (Dutta et al., 2015; Koletzko et al., 2005). In a Cochrane review of VLBW infants, a slower daily increment of 15 – 20 ml/kg/day was compared to faster advancement of enteral feeding (30 – 35 ml/kg/day), and the faster advancement reached full feeds and regained birth weight quicker and did not increase mortality, necrotizing enterocolitis (NEC), or interruption of feedings (Morgan, Young, & McGuire, 2014). Generally, full enteral feeds (150 – 180 ml/kg/day) are reached at day of life 14 in ELBW infants and by day life seven in VLBW infants in those that follow progressive evidence-based feeding guidelines (Dutta et al., 2015).

The practice of delaying initiation or continuation of enteral nutrition is still observed in NICUs (Senterre, 2014). Commonly cited reasons for withholding enteral nutrition include GI immaturity, fear of NEC, perinatal asphyxia, lactic acidosis, patent ductus arteriosus requiring indomethacin or Ibuprofen therapy, postnatal hemodynamic instability requiring inotrope therapy, or presence of an umbilical arterial catheter (Hans, Pylipow, Long, Thureen, & Georgieff, 2009; Klingenberg, Embleton, Jacobs, O'Connell, & Kuschel, 2011). There is no strong evidence that withholding feedings during these clinical situations improves outcomes

(Morgan, Bombell et al, 2013; Morgan, Young, & McGuire, 2013; Neu, 2014; Parker, Neu, Torrazza, & Li, 2013).

In VLBW infants, delayed enteral nutrition is associated with a significant increase in time to reach full enteral feeds, prolonged parental nutrition therapy and parental nutrition associated morbidities, malnutrition, decreased weight gain, slower head growth, increased risk for non-conjugated hyperbilirubinemia, nosocomial sepsis, metabolic disturbances, oxygen needs, and longer time to discharge (Flidel-Rimon et al., 2004; McClure & Newell, 2000; Morgan, Young et al., 2013; Rochow et al., 2012). Morgan, Young et al. (2013) reported in a systematic review, that delaying enteral nutrition beyond four days of life did not decrease risk for NEC in VLBW infants. The known contraindications to enteral nutrition includes intestinal obstruction or ileus (Dutta et al., 2015).

Oral Feeding

There are no universal criteria when preterm infants can begin nonnutritive sucking and feeding at the breast (Donath & Amir, 2008). Gestational age and postmenstrual age alone are not reliable indicators of an infant's suckling and feeding ability (Nyquist, 2008; Nyquist, Sjoden, & Ewald, 1999). Nyquist and Ewald (1999) found in a study of 71 preterm infants born between 27 and 36 weeks gestation that behaviors, including rooting, areolar grasp, and latch, were achieved at 28 weeks postmenstrual age, and nutritive sucking was achieved at 31 weeks postmenstrual age.

There is no evidence that it is required or advantageous to initiate oral feedings with a bottle instead of at the breast (Hoban et al., 2015). Berger, Weintraub, Dollberg, Kopolovitz, and Mandel (2009) reported that in 19 preterm infants born at 32 weeks gestation, there was no difference in maternal milk intake or energy expenditure at the breast compared with bottle

feeding. Casavant, Judge, and McGrath (2017) found that if the first oral feed was direct to the breast, the infant would be more likely to still be receiving breastmilk at discharge. Encouraging mothers to directly provide mother's milk from the breast, in comparison to bottle feeding, can increase likelihood to continue breastfeeding at discharge from the NICU (Briere, Mcgrath, Cong, Brownell, & Cusson, 2015; Casavant et al., 2017).

Demand Feedings

The concept of preterm infant initiated feedings (demand feedings) in response to hunger and satiation cues has promising future when compared to scheduled interval feedings in the NICU. The current practice in the United States is that preterm infants experience scheduled interval feedings (Watson & McGuire, 2016). It is not known if this is an optimal nutrition practice. Watson and McGuire (2016) reported that demand or semi-demand feedings were correlated with earlier achievement of full oral feedings, increased nutrient intake and growth rates, and earlier discharge from the NICU at an average of two to four days.

Semi-demand feedings allow the caregiver to recognize and respond to feeding cues. Semi-demand feeding includes a prescribed 24 hour minimal milk intake (Watson & McGuire, 2016). In general, the prescribed 24 hour milk intake requirement is divided over six to eight hour timeframes. If the infant does not consume the minimum feeding at the breast during that designated time, as evidenced by pre/post feeding weight, the remaining milk volume is administered at the end of the time interval (Watson & McGuire, 2016).

Types of Nutrition

In this section, I will review the types of preterm infant nutrition delivered in the NICU. The types of enteral or oral nutrition that preterm infants may receive, human milk (mothers own milk and/or PDHM) and/or formula, will be reviewed.

Human Milk

Human milk composition has been biologically adapted throughout existence to meet the nutritional and immunological requirements of infants (Riordan & Wambach, 2010). Human milk includes mother's own milk (MOM) or pasteurized donor human milk.

Composition of human milk. Breast milk is a vital source of not only infant nutrition but immune modulating bioactive components to support infant growth and health (Andreas, Kampmann, & Le-Doare, 2015; Martin, Ling, & Blackburn, 2016). Composition of human milk is highly variable and can change within a single feeding or differ between breasts, influenced by diurnal patterns, exclusivity, postnatal age, gestational stage, and within storage and pasteurization of expressed human milk (Riordan & Wambach, 2010). The primary components of human milk include water, lipids, lactose, and protein (Andreas et al., 2015). Secondary components include vitamins, minerals, and bioactive/immune modulating components (Andreas et al., 2015; Martin et al., 2016).

Table 1.

Composition of Major Components of Human Milk

Component	Composition
Lipids	• 40% to 55% of energy supplied from human milk (Andreas et al., 2015; Guo, 2014). • Most variable constituent (Kent, 2007). • Inverse relationship with degree of breast fullness (Kent, 2007). • Maternal diet does not affect the total amount of fat found in human milk; however, the habitual dietary intake of fatty acids is the primary influence on the composition of lipid content with most milk fat (98% to 99%) being comprised of triglycerides (Antonkou et al., 2013).
Lactose	• 40% of energy that is supplied from breast milk (Guo, 2014). • Helps in absorption of iron and calcium in the breastfed infant (Martin et al., 2016). • Plays a crucial role in corresponding to the high energy demands of the infant brain (Andreas et al., 2015).
Protein	• Very low protein content, as it is species-specific and meets the needs of immature kidneys and liver in the human neonate that cannot yet process a high protein milk. • Roles in immunomodulatory and antimicrobial effects (Andreas et al., 20152015). • The primary source of protein in human milk is synthesized by the lactocyte, and the remaining 10% to 20% of protein is obtained via transcytosis from maternal circulation (Andreas et al., 2015).

Mother's own milk. Mother's own milk is defined as human milk provided by the infant's biological mother. Mother's own milk is the food of choice for all preterm infants (Krolak-Olejnik & Czosnykowska-Lukacka, 2017). Mother's own milk contains many bioactive components that are mother-specific, including human milk microbiome probiotic bacteria and prebiotic oligosaccharides (Collado et al., 2015; Underwood et al., 2015). When MOM is not available, PDHM is recommended as a suitable alternative superior to formula (Arslanoglu, Ziegler, & Moro, 2010). Mother's own milk is unique in providing immunoprotection via

antibodies that may be reduced in pasteurization compared to PDHM (Boyd, Quigley, & Brocklehurst, 2007; Tudehope, 2013).

Pasteurized donor human milk. There are many reasons in which MOM is not available or is contraindicated, including maternal disease/surgery/death, maternal use of drugs or certain medications, inadequate supply, cost, or mother's preference. For those mothers of preterm infants that are unable to provide mother's milk, PDHM is a great alternative that offers similar health protections to mother's milk (Vongbhavit & Underwood, 2016). Pasteurized donor human milk utilized in NICUs is human milk supplied by lactating women that is screened and pasteurized at a human milk bank (Arslanoglu et al., 2010). Pasteurization of human milk removes potentially harmful viruses and bacteria, but also alters important protective immunologic and anti-infective properties, including lipase, lymphocytes, immunoglobulin G (Arslanoglu et al., 2010, Boyd et al., 2007; Tudehope, 2013). As a result of pasteurization, it cannot be assumed that PDHM has the same protections as MOM (Boyd et al., 2007).

Researchers have reported that up to 72% of all mothers of very preterm infants in the NICU were unable to provide all mother's milk needed for an exclusive human milk (EHM) diet (Carroll and Herrmann, 2013). Pasteurized donor human milk used to supplement or replace MOM is strongly associated with decreased preterm infant morbidity (Edwards & Spatz, 2012). There is reduced risk for feeding intolerance, NEC, nosocomial infections, respiratory disease, and feeding intolerance with use of PDHM compared to formula (Edwards & Spatz 2012). Kim, Lee, and Chung (2017) found that preterm infants who received a PDHM diet were more likely to reach full feedings earlier compared to formula fed infants (29.6 ± 12.0 vs 52.2 ± 17.6 days).

Comparison of donor milk: full term versus preterm. Postnatal age and gestational stage are important predictors of human milk content. Gidrewicz and Fenton (2014) found that in

comparison of term human milk to preterm human milk, there were statically significant differences in human milk composition, with exception of fat and calculated energy. Human milk bioactive proteins with anti-infective, immune, and neuroendocrine properties and including IgA, lysozyme, and adiponectin were higher in preterm transitional breast milk than in term breast milk (Mehta & Petrova, 2010). Lactoferrin, osteoprotegerin, and leptin were higher in term transitional human milk than in preterm human milk (regression analysis, $p < 0.05$ to 0.0001; Mehta & Petrova, 2010).

There are significant differences in bioactive and true proteins between preterm and term human milk (Gidrewicz & Fenton, 2014; Hsu et al., 2014; Mehta & Petrova, 2010). True protein content in preterm human milk is higher than term milk, with up to 35% difference in true protein content within the first three days of life (Gidrewicz & Fenton, 2014). As postpartum age increases, the difference in true protein content between preterm and term human milk becomes similar within 0.2 g/dL by postpartum day three and the same by weeks 10 to 12 (Gidrewicz & Fenton, 2014). Similarly, Radmacher, Lewis, & Adamkin (2013) found when examining macronutrient content using mid-infrared spectrophotometry, term donor milk had protein concentration of 1 g/dL and 15 kcal/oz compared to preterm mother's milk protein concentration of 1.4 g/dL and 19 kcal/oz. Preterm mother's milk protein changed according to week of lactation, declining over the first three months; however, it was always statistically greater than that found in PDHM (Radmacher et al., 2013).

Formula

While formula substitution efforts have been made, the immunological benefits of human milk have not been duplicated (Ridoran & Wambach, 2010). Formula is an appropriate option for preterm infant nutrition when MOM and PDHM is not available (Tudehope, Page, & Gilroy,

2012). Formula has been commercially designed to provide nutrition that will result in matching intrauterine growth (Tudehope et al., 2012). Preterm infant formula typically provides 80 to 82 kcal/100 mL protein (Tudehope et al., 2012). Formula can offer an advantage of predictable uniform composition.

Despite the known benefits of EHM feedings, health care providers caring for preterm infants continue to supplement human milk with formula to maximize growth acceleration (Hay & Hendrickson, 2017). In a meta-analysis, Wagner (2013) found an average daily weight gain of 2.7 – 3.8 gm/kg greater in preterm infants fed preterm infant formula compared to PDHM fed infants. A Cochrane review examined over 1,000 VLWB infants and compared growth with formula and PDHM (Quigley & McGuire, 2014). In four studies, Quigley and McGuire (2014) compared term formula and PDHM, and in five studies, compared preterm infant formula and pasteurized donor human milk. In only two of these studies, PDHM was fortified. The formula fed preterm infants had higher growth rates for head circumference, length, and weight in all studies (Quigley & McGuire, 2014). Formula in comparison to human milk lacks active enzymes that improve maturation of the preterm gut and anti-infective properties. Formula use in the preterm infant is correlated with later advancement of full enteral feedings, increased risk of NEC, increased duration of parental nutrition, and increased length of NICU stay (Boyd et al., 2007; Hay & Hendrickson, 2017; Quigley, Henderson, & Anthony, 2007).

Fortification of Human Milk

In this section, I will review fortification of human milk. I will examine types of fortifier, fortification methods, and lactoengineering.

Not all research clearly supports fortification of human milk in preterm infants; however, many researchers and neonatal providers argue that MOM and/or PDHM requires fortification to

meet the high nutrient needs in order for preterm infants to achieve optimal growth velocity (McLeod and Sherriff, 2007; Radmacher & Adamkin, 2017; Reali et al., 2015; Schanler, Lau, Hurst, & Smith, 2005). When preterm infants are born in the early third trimester, they miss the placental transfer of nutrients that normally serve as stores for use postnatally (Henriksen et al., 2009). Fortification may provide supplementation of these missing nutritional stores.

The practical guidelines for nutritional care of preterm infants recommends fortification of human milk in both ELBW and VLBW infants prior to reaching 100 mL/kg/day (Senterre, 2014) at a concentration of 1:50 (Dutta et al., 2015). The AAP (2012) recommend that all preterm infants born with a birth weight < 1,500 grams should be fed fortified human milk. The European Society of Paediatric Gastroenteroly, Hepatology, and Nutrition (ESPGHAN) recommends that all preterm infants born with a birth weight less < 1,800 grams should be fed fortified human milk (Agostoni, Buonocore, Carnielli et al., 2010). Fortification of human milk should include proteins, vitamins, and minerals (AAP, 2012; Agostoni et al., 2010). There is not a recommendation made when to stop fortification.

Some researchers argue that unfortified human milk is commonly deficient in at least one or a combination of the three macronutrients: protein, carbohydrates, or fat (Rochow et al., 2013). The primary nutrient deficiency reported in human milk is inadequate protein and energy (kcal) concentration (Arslanoglu, Moro & Zeigler, 2006; Krcho, Vojtova, & Benesova, 2015). The difference between the mean energy concentration of unfortified and fortified preterm human milk was 7.897 kcal/L (Krocho et al., 2015). However, preterm infants fed MOM or PDHM with human milk fortifier, compared to infant formula, may have decreased protein needs, as the bioavailability is greater in fortified human milk (McLeod and Sherriff, 2007).

Two types of fortification are readily available, including donor human milk-based fortifier or a bovine milk-based fortifier.

Types of Fortifier

Donor human milk-based fortifier. Donor human milk based fortifier (Prolacta) is derived from pooled human milk and is available in a variety of products, ranging from 24 cal/oz to 30 cal/oz and can supplement electrolytes and minerals (Radmacher & Adamkin, 2017). Donor human milk-based fortifiers support an EHM diet and have significant implications that may decrease risk for morbidity, mortality, and healthcare costs. Sullivan et al. (2010) reported that preterm infants fed a donor human milk-based fortified human milk diet, compared to those fed bovine-based fortified human milk diet, had a 50% decreased risk for NEC and an 80% decreased risk for requiring surgery secondary to NEC.

Bovine milk-based fortifier. Bovine milk-based fortifier (Enfamil Human Milk fortifier/Similac Human Milk Fortifier) is derived from bovine milk protein and is available in a variety that can add an additional 1.4 g to 2.2 g of protein when four packets are added to 100 mL of human milk (Radmacher & Adamkin, 2017). Bovine fortifier is the most commonly used fortifier in NICUs due to cost. Use of bovine fortifier in human milk exposes the infant to non-human milk protein and is associated with serious health issues, including increased risk of NEC, respiratory infection, sepsis, and overall reduced survival (Sullivan et al., 2010).

The literature describes three nutritional approaches in human milk fortification: standard fixed dose fortification, adjustable fortification using blood urea nitrogen (BUN) to modify fortification dose, and targeted/individualized fortification based on human milk analysis, with supplementation of specific macronutrients as needed. The optimal methods of fortification when required remain uncertain. The available data suggest that if fortification is required, adhering to

an EHM diet with donor human milk derived fortifier can result in appropriate growth and reduce morbidity and mortality (Abrams, Schanler, Lee Martin, Rechtman, & Prolacta Study Group, 2014).

Fortification Methods

There are two methods of fortification, including standard fortification and individualized fortification. Individual fortification includes two subtypes: adjustable fortification and targeted fortification.

Standard fortification. Standard fortification is the most commonly used method for human milk fortification in NICUs (Radmacher & Adamkin, 2017). The current consensus statement on human milk feeding in preterm infants recommends that fortification begins with standard fortification, with advancement to individualized fortification only if growth is inappropriate (Moro, Arslanoglu, Bertino et al., 2015). Standard fortification is based on the assumption that human milk has a protein content of 1.5 g/dL (Radmacher & Adamkin, 2017). A fixed dose of fortifier is added to human milk. Standard fortification does not take into account any caloric or nutrient changes that may occur in the human milk being fortified (Radmacher & Adamkin, 2017).

Some researchers argue that preterm infants fed human milk with standard fortification may not meet the recommended nutrient intake in VLBW infants (Rochow et al., 2013). Arslangoglu et al. (2006) found that standard fortification of human milk with bovine fortifier can still be a deficit in protein intake and lead to slower growth than those fed equicaloric formulas. Henriksen et al. (2009) found that in 127 VLBW infants fed preterm mother's milk or donor human milk with standard fortification at 120 ml/k/day still demonstrated growth failure at discharge, defined as body weight less than the 10th percentile, in 58% of the sample. In

contrast, Ginovart, Gich, Gutierrez, and Verd (2017) examined weight gain and head growth in VLBW preterm infants fed standard fortified (80 ml/kg/day) MOM or PDHM compared to formula fed infants, and extrauterine growth was significantly greater in the infants fed the standardized fortified human milk diet.

Adjustable fortification. Adjustable fortification utilizes preterm infant BUN level to modify fortification dose (Radmacher & Adamkin, 2017). The BUN measures serve as a proxy for assessing adequate protein intake (Radmacher & Adamkin, 2017). The amount of fortifier added to human milk is dependent on changes in serial BUN measurements obtained twice-weekly (Arslanoglu et al., 2006). If BUN is lower than threshold, additional fortifier is supplemented, and if BUN is greater than desired, the amount of fortifier is reduced (Radmacher & Adamkin, 2017).

Arslanoglu et al. (2006) found adjustable fortification with bovine fortifier and aggressive protein supplementation based on infant BUN levels superior, with significantly greater growth (weight, head circumference, and growth velocity) compared to standard fortification (bovine fortification of 5g/100ml of human milk). Adjustable fortification with bovine fortifier had an average growth velocity of 17.5 $\pm$ 3.2 gm/kg/day compared to standard fortification with bovine fortifier 14.4 $\pm$ 2.7 gm/kg/day (Arslanoglu et al., 2006). Arslanoglu et al. (2006) reported that the consequence of standard fortification was protein under nutrition resulting in decreased growth.

Targeted fortification. Targeted fortification utilizes human milk analysis to inform providers what type of supplementation is needed to closely match an infant's diet with nutritional needs for adequate growth and development (Radmacher & Adamkin, 2017). Targeted fortification can be accomplished by addition of fortifiers or lactoengineering of milk.

With use of fortifiers, the preterm infants recent growth rate on the current fortification regime and macronutrient analysis of human milk are taken into consideration (Radmacher & Adamkin, 2017). Studies have shown that targeted fortification of human milk provides increased protein and is correlated with exceeding the expected growth velocity of 15 gm/kg/day, improving short term weight gain, and increasing linear growth (Hair et al., 2014, Reali et al. 2015; Rochow et al., 2013).

Lactoengineering

Lactoengineering of human milk is an alternative to fortification of human milk. Lactoengineering utilizes high fat milk cream that rises to the top of the milk sample (Hair et al., 2014; Ogechi et al., 2007, Slusher et al., 2003). The high fat cream is skimmed off the top to be provided to the infant to increase fat and energy content (Hair et al., 2014). Engineering human milk with human milk-derived cream supplement using the Creamatocrit technique can provide energy dense feedings without substantial increase in the total volume of feeds (Hair et al., 2014). Hair et al. (2014) found in a randomized control trial, when VLBW infants are given MOM or PDHM lactoengineered with human milk-derived cream product, compared with standard bovine milk fortifier, the human milk-derived cream product had significantly enhanced growth velocity. Infants who received human milk-derived cream product had an average growth velocity of 14.0 gm/kg/day (Hair et al., 2014). Infants who received standard bovine milk-fortified diet had an average growth velocity of 12.4 gm/kg/ day (Hair et al., 2014).

Cost of Human Milk Use in the NICU

In this section, I review cost of human milk use in the NICU. I specifically examine the potential cost savings attributed to use of human milk in the NICU by decreasing preterm infant morbidity/mortality risk (Buckle & Taylor, 2017).

The AAP (2017) reported that use of PDHM is limited by availability and purchase cost. Hospitals that use banked donor milk generally have minimal budgets allocated for purchase of donor milk (National Breastfeeding Center, 2016). Donor human milk costs on average $4.50 per ounce incurred as processing fee (Huertas, 2015; Spatz, Robinson, & Froh, 2017). The processing fee covers costs to screen potential donors, including laboratory costs, processing human milk, shipping, supplies, and general overhead incurred in running a nonprofit milk bank (Spatz et al., 2017). However, for every $1.00 spent on pasteurized donor human milk, there is a potential saving up to $11.00 in medical costs of the preterm infant (Huertas, 2015).

The potential long-term cost savings by adhering to an EHM diet and avoiding bovine fortifier and bovine formula is profound among preterm infants in the NICU. In avoidance of NEC alone, Ganapathy, Hay, and Kim (2012) reported a lower expected NICU length of stay of 3.9 NICU days and reduced total expected costs of hospitalization with a net direct average savings of $8,167.17 per extremely premature infant (multivariate regression, $p < 0.0001$). Buckle and Taylor (2017) stated that the estimated increased incremental length of stay associated with NEC was 18 days for medical management of NEC and 50 days for management of surgical NEC. Necrotizing enterocolitis is among the highest per case cost for commercial insurance and Medicaid and a huge cost driver in NICUs (Bisquera, Cooper, & Berseth, 2002). Necrotizing enterocolitis accounts for 19% of NICU expenditures and $5 billion per year in hospitalization costs (Bisquera et al., 2002). Human milk is the only treatment known to reduce the incidence of NEC (Bisquera et al., 2002). Human milk reduces risk for NEC by 77% (Bisquera et al., 2002). Future research should include full economic evaluation to examine longitudinal outcomes related to preterm infant nutrition cost and morbidity/mortality risk (Buckle & Taylor, 2017).

Current Recommendations for Preterm Infant Feeding and Growth

Human milk is regarded as the superior and preferred feeding method for hospitalized preterm infants (Menon & Williams, 2013). All preterm infants should receive human milk, and if MOM is not available or contraindicated, PDHM should be used (AAP, 2012). Preterm infants who are clinically stable and able to breastfeed should be introduced to the breast as soon as possible and exclusively breastfed for six months (AAP, 2012). Exclusive human milk diet in the hospitalized extremely preterm infant is associated with lower risks of death, NEC, and sepsis (Abrams et al., 2014). Exclusive human milk diet for preterm infants has been identified as one of the most influential preventative treatments available in NICUs that reduce infant morbidity and mortality (National Breastfeeding Center, 2016).

Body composition is a key metric when assessing nutrition in preterm infants; however, widespread use body composition measures in NICUs are limited due to cost and feasibility (Kiger et al., 2016). Due to these limitations, anthropometric measures are very useful and a necessary tool for neonatal care providers in prescribing preterm infant nutrition (Kiger et al., 2016). Accurate daily weights, weekly lengths and head circumferences should be obtained in all hospitalized preterm infants (Anderson, 2014; Greer & Olsen, 2013; Poindexter, 2014). These measures should be plotted on a standardized growth chart at the same time each week during the NICU stay to inform nutritional practices (Anderson, 2014, Greer & Olsen, 2013; McLeod & Sherriff, 2007).

Gaps in Knowledge

The current state of the science on preterm infant growth and nutrition does not provide researchers or clinicians with sufficient data to determine optimal growth for each individual infant (Embleton et al., 2017). Preterm infant growth is multifactorial based on maternal and

infant physiological, developmental, genetic, nutritional, and environmental factors that can greatly differ between each infant. It is apparent that an intrauterine rate of growth for one preterm may be sufficient, but a slower trajectory may be more appropriate for a different infant (Embleton et al., 2017). Further research studies are needed to address if NICU growth velocity goals should be redefined. The failure of many infants to achieve the desired growth velocity may indicate inadequacy of the current standard.

Nutritional management of preterm infants is marked by a lack of practice uniformity (Wight et al., 2008). Despite existing standardized feeding guidelines there continues to be significant heterogeneity within and between NICUs in type, timing, and frequency in delivery of preterm infant nutrition from the first hour of life to NICU discharge (Ehrenkranz, 2014; Wight et al., 2008). Interventions for preterm infants that utilize standardized feeding protocols are not well represented in the literature (Butler et al., 2013). Future research should include specific nutrient and fortification composition to promote growth.

There is not a clear understanding of the consequences of rapid growth. It is possible that lower nutrient intake and slower growth may be protective longitudinally (Embleton et al., 2017). Future research is needed to examine the relationship between fetal and neonatal growth and alteration of subsequent metabolic and cardiac function to prevent risk for harm later in life.

Summary

It is unclear what optimal growth and associated nutrition is for preterm infants. It is possible that if a preterm infant's growth appears stable and is moving appropriately across percentiles, and there is no underlying contributing pathology, then quite possibly, this may be optimal (Embleton et al., 2017). What is clearly known is that preterm infants fed an EHM diet demonstrate improved morbidity compared to formula fed infants (National Breastfeeding

Center, 2016). Despite many uncertainties in neonatal growth and nutrition, there is a clear relationship between improved health outcomes and a protective dose response relationship with the duration and/or exclusivity of human milk (Embleton et al., 2017). More attention needs to be focused on the quality of growth through optimal nutrition management (McLeod & Sherriff, 2007).

Chapter IV: Methodology

Research Design

A retrospective, descriptive, correlational study was conducted comparing growth of VLBW hospitalized preterm infants by proportion of human milk intake. The study was performed at a level three neonatal intensive care unit in a small urban community in southeast Wisconsin that serves an economically and racially/ethnically diverse community.

Sample

The participants consisted of a convenience sample of VLBW preterm infants. Inclusion criteria included infants born < 1500 gm by vaginal or cesarean birth at study hospital or transferred to study hospital within 12 hours of birth. The exclusion criteria were as follows: infants who died or were transferred prior to reaching full enteral feedings or infants born with visible structural congenital anomalies due to their potential for special nutritional needs and additional health concerns. Visible congenital anomalies were identified according to the International Classification of Diseases found in the problem list of the infant's chart. Participants included 143 preterm infants with birth weights < 1500 gm admitted to the study hospital by birth or transferred within 12 hours after birth. Three infants were excluded for congenital anomalies, 36 infants died, and 22 infants were transferred to a different hospital before reaching full enteral feeding and were excluded from the study. The data from the remaining 82 infants were analyzed.

Power analysis with the 82 infants available for statistical correlational analysis revealed the study was underpowered. Power analysis with an alpha of 0.5, medium effect 0.25, n=82 resulted in a power of .63. While the results of the study may not have been statistically significant, it was felt there would be clinical significance and would be acknowledged as a limitation of the study. The sample size at this single site was not able to be increased as there

was a change in electronic health record (EHR) systems and the data was unavailable for abstraction.

Procedure

Data were abstracted from the EHR from the sample population based on inclusion and exclusion criteria. Data collection forms were created for the purpose of this study to abstract participant characteristics and clinical measures. Data collection was conducted for each subject until full enteral feedings were reached. Data were stored in an electronic format on a password-protected computer. To examine the data for accuracy, the primary investigator performed double data entry on a random sample of 10 cases to check for degree of accuracy compared to original data, and there was 100% agreement.

Protection of Human Subjects

Institutional Review Board (IRB) approval was obtained prior to data collection from the hospital system as the IRB of record and through an agreement with University of Wisconsin Milwaukee IRB. Expedited review and waiver of informed consent was granted because there was minimal risk to infants participating in the retrospective chart review. The primary investigator completed appropriate IRB modules through CITI.

Measurements/Variables

Demographic variables. Demographic variables obtained were race, sex, and type of gestation (singleton or multiple).

Day of life one. Day of life one was measured as day of birth.

Day of first enteral feeding. Day of first enteral feeding was measured as the day of life that enteral feeding was initiated.

Gestational age. Gestational age was measured by prenatal ultrasound obtained before 20 weeks and/or number of weeks dating from the first day of the mother's last menstrual period and/or and infant assessment. Gestational age was measured at birth.

Time to full enteral feeding. Time to full enteral feeding was measured in number of days from day of life one (birth) to 72 hours after the last intake of total parental nutrition (TPN) or parental fluids. Each day of life was measured in calendar days from hours 0000 to 2400. Time to full enteral feeding was measured as 72 hours after last intake of TPN of parental fluid intake to ensure the infant would successfully tolerate the transition of increased enteral feedings.

Type and amount of nutritional intake. Human milk intake refers to MOM and pasteurized donor human milk. All intake that is not human milk intake is considered preterm infant formula. Mother's own milk refers to human milk produced by the mother of the preterm infant. Pasteurized donor human milk (PDHM) refers to human milk expressed by milk donors and provided by Mother's Milk Bank of Western Great Lakes. Both preterm and term PDHM were available at the hospital of study, however, the EHR does not indicate what type of PDHM was used in each individual infant or at each individual feeding. Nutritional intake was abstracted for each feeding separately until the infant reached full enteral feedings.

Fortification of Pasteurized Donor Human Milk. Fortification of PDHM was performed with standard fortification, adding a fixed dose commercial fortifier to human milk. There was not a standardized protocol for fortification initiation and advancement used at this study site and varied among provider preference.

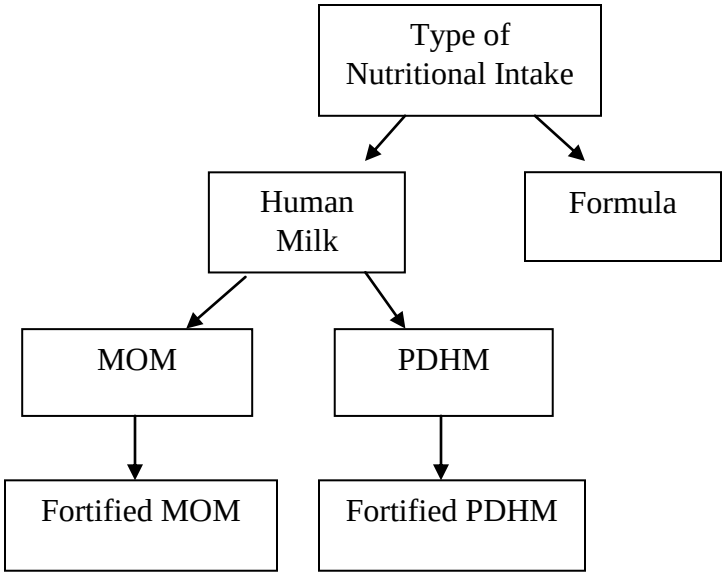

Figure 3. Stratification of type of nutritional intake.

Volume of enteral intake at time of human milk fortification. In the subgroup of infants who experienced fortification of human milk, volume of enteral intake at the time of fortification initiation was abstracted. Volume of enteral intake was calculated as mL/kg/day on the day fortification was initiated.

Growth velocity. Growth velocity is a measure used to summarize infant weight gain over a specific time interval (Patel et al., 2009). Estimated growth velocity (gm/kilogram/day) was measured using an exponential model (EM). The EM is validated for use in VLBW infants to examine growth (Patel et al., 2009). The EM (W= weight in grams, D= day, 1 beginning time interval and n = end of time interval in days) is:

$$GV = [1000 \times \ln(Wn/W_1)]/(D_n - D_1)$$

Growth velocity at time of human milk fortification. In the subgroup of infants who experienced fortification of human milk, growth velocity (gm/kg/day) was examined at the time of fortification initiation.

Growth by feeding type. Growth velocity (gm/kg/day) for postmenstrual age from birth through full feeding was measured by quantity of human milk intake. Subgroup analysis of growth based on feeding type was performed between mother' own milk, pasteurized donor human milk, fortified MOM, and PDHM (see Figure 4).

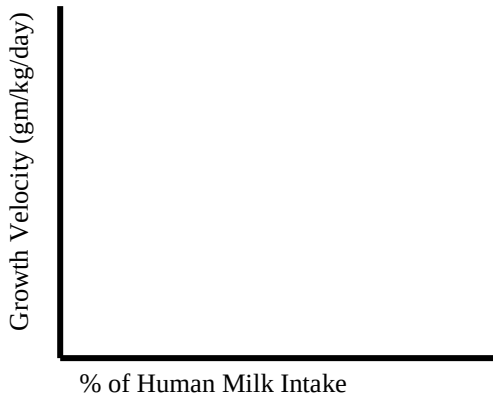

Figure 4. Growth velocity by percent of human milk intake

Weight. Weight was recorded as measured in the EHR. Weight is measured at this facility using the Olympic Smart Scale. The Olympic Smart Scale provides an electronic biophysical objective measure of weight in grams. The Olympic Smart Scale is a reliable and valid measure of preterm infant weight for calculation of medications, parental fluids, and nutritional requirements (Engstrom et al., 1995). Engstrom et al. (1995) determined reliability by obtaining two weight measurements by two nurses for each infant (N=32) for three consecutive days. The intraexaminer reliability was determined by examining the difference between each nurse's weight measurements. The average mean absolute difference between individual nurse's weight measurements was 12.58 grams for weights obtained in the incubator and 19.19 grams for weights obtained with the radiant warmer (Engstrom et al., 1995). The interexaminer reliability was determined by examining the difference between the pairs of nurses' weight measurements. The average mean absolute difference was 14.29 grams for weights obtained in the incubator and

24.42 grams for weights obtained with the radiant warmer (Engstrom et al., 1995). According to the NICU policy at the institution of study, weight should be measured on day of life one and, thereafter, every 3 days until discharge from the NICU.

Suboptimal growth. Suboptimal growth was measured as growth velocity less than 15 gm/kg/day.

Table 2.

Measure and Data Management Chart

Research Question	Variable	Measurement	Level of Measurement	Statistical Test
What is the growth velocity (gm/kg/day) of VLBW preterm infants at the time human milk fortification is initiated?	**IV**- time of human milk fortification **DV**- growth velocity	Time of human milk fortification initiation= day of life that human milk fortification was initiated GV = [1000 × ln(Wn/W_1)]/($D_n - D_1$) W= weight in grams D= day, 1 beginning time interval n= end of time interval in days Weights as they were obtained every 1-5 days will be used to calculate GV. These GV values will then be averaged over the NICU time to full feedings to yield the overall GV.	Time of human milk fortification initiation- interval Growth velocity (gm/kg/day)- interval level.	Descriptive analysis
Is there a relationship between growth velocity (gm/kg/day) of VLBW preterm infants from birth to full feeding and percentage of human milk intake?	**IV**- percentage of human milk intake **DV**- growth velocity (gm/kg/day)	% of human milk intake= human milk intake/ total intake GV = [1000 × ln(Wn/W_1)]/($D_n - D_1$)	Percentage of human milk intake- interval Growth velocity (gm/kg/day)- interval	Correlational analysis
Is there a relationship between growth velocity (gm/kg/day) of VLBW preterm infants from birth to full feeding and percentage of mother's own milk, pasteurized donor milk, and mixed donor/ mother's own milk intake?	**IV**- percentage of mother's own milk, pasteurized donor milk, and mixed donor/ mother's own milk intake **DV**- growth velocity (gm/kg/day)	% of human milk intake= human milk intake/ total intake GV = [1000 × ln(Wn/W_1)]/($D_n - D_1$)	Percentage of human milk intake- interval Growth velocity (gm/kg/day)- interval	Correlational analysis
What is the volume of enteral intake (mL/kg/day) at the time human milk fortification is	**IV**- time of human milk fortification **DV**- volume of enteral intake	Time of human milk fortification= day of life that human milk fortification was initiated Volume of enteral intake	Time of human milk fortification- interval Volume of enteral	Descriptive analysis

initiated?		(mL/kg/day)	intake- interval	
What is the average day of life when birth weight is regained?	**Descriptive-** day life birth weight is regained	Day of life that when birth weight is regained	Day of life- interval	Descriptive analysis
What is the average day of life that enteral feedings are initiated?	**Descriptive-** day of life that enteral feedings are initiated	Day of life when enteral feedings are initiated	Day of life- interval	Descriptive analysis
What percentage of infants experience sub-optimal growth as measured by a growth velocity < 15gm/kg/day when reaching full feedings in the NICU?	**Descriptive-** percentage of infants with suboptimal growth	% of sample with growth velocity less than 15gm/kg/day when reaching full feedings	% of sample with growth velocity less than 15gm/kg/day - ratio	Descriptive analysis

Data Management Plan

The primary investigator acted as the data manager with the biostatistician when implementing the data management plan. A biostatistician provided consultation during data analysis. The data management plan included the following steps:

1. All patients were coded to ensure confidentiality. A list of patient name and MRN were coded to a subject number and maintained during the study. The file was electronic password-protected. Subject identification numbers (ID) were used with data collected from patient charts. These were stored in an electronic format on a password-protected computer for only study personnel to access. Study data was only made available to study investigators.
2. The primary investigator entered all the data into a password-protected database in SPSS® statistics 23 and created a code book.
3. The data was screened for errors. First, data was checked to make sure all scores were not out of range for each categorical and continuous variable using SPSS®

statistics 23. Errors were corrected. The process was repeated until there was confidence that the data was clean. A log book of all errors in the data were recorded.

4. After 25% of the data was abstracted and entered, the sample demographics were checked for errors or skew and assumptions were checked.
5. Data was appropriate and assumptions were met and the remaining data was abstracted and analyzed.
6. The data file was examined for missing data. Descriptives were run to examine what percentage of values were missing in each variable. Missing data was checked for patterns. Missing values were managed by excluding cases pairwise. By excluding cases pairwise, the subject was only excluded if the data was required for a specific analysis ran. The subject was included in any analysis where they had the required data. This was beneficial to keep sample size adequate.
7. The statistical team at the university of study, methodological experts, and the primary investigator collaborated and discussed any issues and need for modifications.

Analysis

Participant characteristics and clinical variables were analyzed for frequencies, frequency distributions, percentages, mean, median, and standard deviation. The descriptive statistics of these variables were examined for skewness, kurtosis, normality, and missing data. The descriptive statistics were used to describe the characteristics of the sample and address all research questions.

All analyses were performed using SPSS® statistics 23. Initially, descriptive statistics were analyzed. Frequencies, frequency distributions, and percentages were run on categorical

variables. Descriptive statistics, including frequencies, mean, median, and standard deviation, were run on the descriptive variables. The descriptive statistics of these variables were examined for skewness, kurtosis, normality, and missing data. The descriptive statistics were used to describe the characteristics of the sample and to address the descriptive research questions.

To examine the non-descriptive research questions, a correlation was performed. A correlation is an appropriate statistical test, as the purpose of the research was to explore the strength of the relationship between percent of human milk intake (continuous variable) and growth velocity (continuous variable).

The assumptions for correlation and Pearson product-moment correlation coefficient were checked for violations, including level of measurement, related pairs, normality, linearity, and homogeneity of variance. The level of measurement was met, as both variables are continuous. Related pairs were met, as each participant had a pair of values for each variable. Normality was examined with the Komogorov-Smirnov test. There was not a Sig. value less than 0.70, indicating normality. Lastly, linearity and homoscedasticity were examined. Linearity and homoscedasticity were not met. The shape of the values formed by the scatterplot were nonlinear in a blob-type arrangement. After consideration and discussion with a biostatitisican, it was decided to abandon correlation analysis and to move forward with analysis of the descriptive research questions.

Chapter V: Study Results

The objective of this study was to examine how feeding practices impact growth in hospitalized preterm infants < 1500 grams from birth until reaching full enteral feedings. In addition, this study explored growth velocity rates associated with clinician initiation of fortification of preterm infant human milk feedings. The following section of Chapter 5 presents a manuscript, "Preterm Infant Growth and Human Milk Exposure in the NICU" for submission to and possible publication in the *Journal of Obstetric Gynecologic and Neonatal Nursing*, presenting the study results and synthesis of findings.

Preterm Infant Growth and Human Milk Exposure in the NICU

Abstract

Objectives: Examine how feeding practices impact growth in infants less than 1500 gm from birth until reaching full enteral feedings. Identify growth velocity rates associated with clinician initiation of fortification of preterm infant human milk feedings.

Design: Retrospective descriptive study.

Setting: Level 3 neonatal intensive care unit in a small urban community in Southeast Wisconsin**.**

Participants: A convenience sample of 82 very low birth weight preterm infants who were born with birth weight < 1500 gm, vaginal or cesarean birth, born at study hospital or transferred to study hospital within 12 hours of birth.

Methods: Data were collected from the participant's electronic health records from birth until the infant reached full enteral feedings.

Results: 82 preterm infants with a mean gestational age 29.30 weeks (*SD* 3.11) and mean birth weight 1108.84 gm (*SD* 272.77) were included. In those infants who received fortification of mother's own milk and/or pasteurized donor human milk (53.7%), mean growth velocity was 3.89 gm/kg/day (*SD* 12.76) and mean volume of enteral intake was 132.60 mL/kg/day (*SD* 28.29). When reaching full feeding, mean growth velocity was 0.15 gm/kg/day (*SD* 11.09).

Conclusions: Initiation of human milk fortification or lactoengineering earlier in development may have prevented or decreased extent of growth failure, as evidenced by growth velocity less than 15 gm/kg/day when reaching full enteral feedings.

Keywords: Preterm infant growth, growth velocity, growth failure, fortification, human milk

Background

Most health care providers strive to prescribe nutritional practices in the neonatal intensive care unit (NICU) to achieve growth comparable to intrauterine life (Hay, 2013; Kleinman & American Academy of Pediatrics [AAP], 2009; Puntis, 2006). The recommended standard intrauterine growth rate is 15 gm/kg/day (Kleinman & AAP, 2009). Intrauterine growth is accepted as the standard measurement for extrauterine growth for preterm infants because a superior growth standard remains undefined (Fenton & Kim, 2013). As preterm infants are not a homogenous group, a major conceptual flaw is created when using a standard growth rate to define optimal growth (Embleton, Cleminson & Zalewski, 2017). Preterm infant growth is multifactorial based on maternal and infant physiological, developmental, genetic, nutritional, and environmental factors that differ in each preterm infant. As these variables differ among preterm infants, it is apparent that an intrauterine rate of growth for one infant may be sufficient, but a slower trajectory may be more appropriate and biologically plausible for the next infant (Embleton et al., 2017).

Growth failure has consequences for short- and long-term infant health. Preterm infant growth failure is associated with adverse neurodevelopmental outcomes and somatic development, longer NICU stay, and potentially preventable morbidities (McLeod & Sherriff, 2007; Vasu & Modi, 2007; Walker, Keene, & Patel, 2014). Growth failure in preterm infants and subsequent infant catch-up growth is related to increased risk for disease in adulthood, including decreased insulin sensitivity, increased insulin resistance, altered adipose tissue metabolism (Finken et al., 2006), obesity, and hypertension (Thomas et al., 2011). The risks associated with growth failure or contrary, rapid catch-up growth has potential health implications that must be weighed heavily when evaluating goal growth standards.

It is unclear what combination of neonatal nutrition is most highly associated with optimal preterm infant health, growth, and development (Rice & Valentine, 2015). Nutrition management to produce adequate growth of preterm infants remains one of the most challenging aspects of care. The types, amounts, and frequencies of feedings administered during initial hospitalization have important implications for future infant growth and development of preterm infants.

Human milk is the preferred feeding for preterm infants (Menon & Williams, 2013; Moro et al., 2015). Supplementation of human milk is quickly and frequently instituted in NICUs with bovine fortification and/or formula to maximize growth acceleration (Menon & Williams, 2013). When preterm infants are born in the early third trimester, they miss the placental transfer of nutrients that serve as stores for postnatal use (Henriksen et al., 2009). Fortification may provide supplementation of missing nutritional stores in the preterm infant. Significant controversy continues among health care professionals about how human milk should be fortified or lactoengineered to support optimal growth (Menon & Williams, 2013).

The practical guidelines for nutritional care of preterm infants recommends fortification of human milk in both extremely low birth weight (ELBW) and very low birth weight (VLBW) infants when they reach feedings at 100 mL/kg/day (Senterre, 2014) at a concentration of 1:50 (Dutta et al., 2015). The AAP (2012) recommends that all preterm infants born < 1500 gm should be fed fortified human milk. The European Society of Paediatric Gastroenteroly, Hepatology, and Nutrition recommends that all preterm infants born less < 1800 gm should be fed fortified human milk (Agostoni et al., 2010).

Objectives

Our research objective was to examine how feeding practices impact growth in hospitalized preterm infants < 1500 gm from birth until reaching full enteral feedings. We planned to explore growth velocity rates associated with clinician initiation of fortification of preterm infant human milk feedings.

Methods

Design and Setting

This study was a retrospective descriptive design, conducted between July 1, 2013 and June 30, 2017, at a Level 3 NICU in a small urban community in Southeast Wisconsin that serves an economically and racially/ethnically diverse community. Institutional Review Board (IRB) approval was obtained prior to data collection from the hospital system as the IRB of record and through an agreement with University of Wisconsin Milwaukee IRB. Expedited review and waiver of informed consent was granted because there was minimal risk to infants participating in the retrospective chart review.

Participants

The participants consisted of a convenience sample of VLBW preterm infants. Inclusion criteria included infants born < 1500 gm by vaginal or cesarean birth at study hospital or transferred to study hospital within 12 hours of birth. The exclusion criteria were as follows: infants who died or were transferred prior to reaching full enteral feedings or infants born with visible structural congenital anomalies due to their potential for special nutritional needs and additional health concerns. Visible congenital anomalies were identified according to the International Classification of Diseases found in the problem list of the infant's chart. Participants included 143 preterm infants with birth weights < 1500 gm admitted to the study

hospital by birth or transferred within 12 hours after birth. Three infants were excluded for congenital anomalies, 36 infants died, and 22 infants were transferred to a different hospital before reaching full enteral feeding and were excluded from the study. The data from the remaining 82 infants were analyzed.

Measures

Participant characteristics. We collected characteristics including sex, single or multiple gestation, ethnicity, gestational age, length, weight, and head circumference at time of birth. Type and amount of nutritional intake was recorded from each feeding from birth until the infant reached full enteral feedings.

Growth velocity. Growth velocity was a measure used to summarize infant weight gain over a specific time interval (Patel, Engstrom, Meier, Jegier, & Kimura, 2009). Growth velocity (grams/kilogram/day) was measured using an exponential model (EM). The EM is validated for use in all VLBW infants to examine growth (Patel et al., 2009). The EM is growth velocity = $[1000 \times \ln(Wn/W_1)]/(D_n - D_1)$, where W = weight in grams, D = day, 1 beginning time interval and n = end of time interval in days (Patel, Engstrom, Meier, & Kimura, 2005). Growth velocity was calculated over multiple time intervals: birth to time of fortification initiation, regain to birth weight to time of fortification initiation, birth to full enteral feedings, and regain to birth weight to full enteral feedings. Weight measurements used to calculate growth velocity were abstracted as recorded in the electronic health record (EHR). According to the NICU policy at the institution of study, weight should be measured on day of life one and thereafter every 3 days until discharge from the NICU.

Time to full enteral feeding. Time to full feeding was measured in number of days from day of life one (birth) to 72 hours after the last intake of total parental nutrition (TPN) or parental fluids. Each day of life is measured in calendar day hours from 0000 to 2400.

Time to fortification. Time to fortification was measured in number of days from day of life one (birth) to day of life that human milk fortification was initiated.

Volume of enteral intake at time of fortification. Volume of enteral intake was measured as ml/kg/day on the day fortification was initiated.

Procedures

Data were abstracted from the EHR from the sample population based on inclusion and exclusion criteria. Data collection forms were created for the purpose of this study to abstract participant characteristics and clinical measures. Data collection was conducted for each subject until full enteral feedings were reached. Data were stored in an electronic format on a password-protected computer. To examine the data for accuracy, the primary investigator performed double data entry on a random sample of 10 cases to check for degree of accuracy compared to original data, and there was 100% agreement.

Statistical Analyses

All analyses were performed using SPSS® statistics 23. Participant characteristics and clinical variables were analyzed for frequencies, frequency distributions, percentages, mean, median, and standard deviation. The descriptive statistics of these variables were examined for skewness, kurtosis, normality, and missing data. The descriptive statistics were used to describe the characteristics of the sample and address all research questions.

Results

Sample Characteristics

Eighty-two preterm infants with a mean gestational age of 29.30 weeks (*SD* 3.11) and mean birth weight of 1108.84 gm (*SD* 272.77) were included in analyses. Mixed mother's own milk (MOM), pasteurized human donor milk (PDHM), fortified MOM, and fortified PDHM composed 92.5% (*SD* 21.9) of the mean individual participant's diet. The primary intake was MOM 53.69% (*SD* 35.75). Mean day of life at first enteral feeding was 2.07 days. Participant characteristics are described in Table 1.

(Table 1)

Seventy-four of 82 (90.24%) infants experienced a growth velocity less than 15 gm/kg/day at full feedings when calculated from birth weight to full feedings. Forty-eight of 82 (58.54%) infants regained birth weight prior to reaching full feedings. Birth weight was regained at a mean of 10.12 (*SD* 3.55) days. Among this subgroup, 22 of 48 (45.8%) infants experienced growth velocity less than 15 gm/kg/day after regaining birth weight to full feedings. Of the infants studied, 44 (53.7%) received fortification of human milk and experienced a mean growth velocity of 3.89 gm/kg/day (*SD* 12.76) at the time of fortification initiation. Human milk fortification did not produce growth to maintain or exceed recommended growth velocity of 15 gm/kg/day from the time of fortification to full feedings. Among the subgroup of infants who received fortified human milk, their mean growth velocity was 0.15 gm/kg/day (*SD* 11.09) at the time they reached full feeding (Figure 1). Participant growth velocity is described in Table 2.

(Figure 1)

(Table 2)

Forty-four (53.7%) infants received fortified human milk prior to reaching full feedings. Human milk fortification was initiated at a mean of 14.0 (*SD* 5.8) days. Mean volume of human milk intake at the time of fortification initiation was 132.61 mL/kg/day (*SD* 28.3; see Figure 2).

(Figure 2)

Discussion

Among the 82 preterm infants in our sample, mean growth velocity was 1.71 gm/kg/day from birth to time of full enteral feeding. Of the 82 participants, only eight participants (9.76%) experienced a growth velocity greater than 15 gm/kg/day. The reported frequency for those infants who experienced growth failure, growth velocity rates less than 15 gm/kg/day (Greer & Olsen, 2013; Griffen, 2017), were consistent with those reported in the literature. Dusick et al. (2003) reported approximately 90% of VLBW infants are classified as having experienced growth failure by 36 weeks corrected gestational age. Malnutrition and subsequent growth failure in preterm infants that occurs during the postnatal period can impact both the function and structure of the brain (Uauy & Mena, 2001). Impeded brain growth can result in irreversible neurodevelopmental deficits, including abnormal motor and cognitive function (Butler, Szekely, & Grow, 2013; Embleton & Tinnion, 2009; McLeod & Sherriff, 2007; Walker et al., 2014). The severe growth failure that occurred in this sample of preterm infants is likely multifactorial. Some of the factors that may have contributed to the severe growth failure include the delay to initiate enteral feedings, delay to initiate fortification, feeding protocol at the hospital of study, and appropriateness of the current growth recommendations.

In this study, enteral feedings were initiated at mean 2.07 days of life. Recommended initiation of enteral nutrition in ELBW and VLBW infants is between six and 48 hours of life (Senterre, 2014), preferably within 24 hours of life (Dutta et al., 2015; Embleton et al., 2017).

Initiation of enteral nutrition is important to prevent gastrointestinal (GI) mucosal dysfunction and atrophy by priming the gut and promoting maturation of the GI system (Neu, 2007). Early introduction of enteral nutrition compared to fasting in VLBW infants is associated with decreased time to reach full enteral feeds, increased weight gain, increased head growth, and decreased time to discharge (Flidel-Rimon et al., 2004; Morgan, Young, & McGuire, 2013). Commonly cited reasons for withholding enteral nutrition include gastrointestinal immaturity, fear of necrotizing enterocolitis, perinatal asphyxia, lactic acidosis, patent ductus arteriosus requiring indomethacin therapy, postnatal hemodynamic instability, or presence of an umbilical arterial catheter (Hans, Pylipow, Long, Thureen, & Georgieff, 2009; Klingenberg, Embleton, Jacobs, O'Connell, & Kuschel, 2011). Intestinal obstruction or ileus are the only absolute contraindications to feeding (Dutta et al., 2015). It is unknown in this sample why initiation of enteral feedings was delayed.

Mean volume of human milk intake at the time of fortification initiation was 132.61 mL/kg/day (*SD* 28.3). Fortification initiation was delayed and not started at the suggested initiation when the infant reaches intake of 100 mL/kg/day (Dutta et al., 2015). Delay to initiate fortification, specifically in the donor human milk group, may have contributed to growth failure.

There was no standardized protocol for fortification initiation and advancement used in this study. Standard fortification, adding a fixed dose fortifier to human milk, was utilized and may have provided insufficient protein, calories, or fat (Arslanoglu, Moro & Zeigler, 2006; Krcho, Vojtova, & Benesova, 2015). Despite fortification, the participants in this study experienced growth failure. In the subgroup of infants who experienced fortification (n = 44), the growth velocity was 3.89 gm/kg/day at the time of fortification initiation, and the growth

velocity was 0.15 gm/kg/day at time of full feeding, suggesting they were barely growing. Similar findings are present in the literature.

Henriksen et al. (2009) examined growth in 127 VLBW infants who received initiation of enteral feedings on the first or second day of life and experienced fortification initiation of MOM or PDHM when achieving enteral intake of 120 ml/kg. Of the infants studied, 58% demonstrated growth failure at discharge (Henriksen et al, 2009). The current consensus statement on human milk feeding in preterm infants recommends that fortification begins with standard fortification, 5 gm/100 ml of human milk providing 0.8 g of protein, with advancement to individualized fortification if growth is inappropriate (Moro et al., 2015). Arslanoglu et al. (2006) found individualized fortification with bovine fortifier and aggressive protein supplementation based on infant blood urea nitrogen levels safe and effective up to 1.8 gm of protein, with significantly greater weight, head circumference, and growth velocity. Adjustable fortification with bovine fortifier had an average growth velocity of 17.5 ± 3.2 gm/kg/day compared to standard fortification with bovine fortifier 14.4 ± 2.7 gm/kg/day (Arslanoglu et al., 2006).

At our study site, the feeding protocol included scheduled interval feedings every four hours. While we did not analyze data on the frequency of feeds for this sample, it should be acknowledged that the feeding protocol at the study site did not follow recommended practices. In infants weighing less than 1250 gm, feedings should be administered at three hour intervals (Dutta et al., 2015). It may even be advantageous to feed preterm infants weighing greater than 1250 gm at two-hour intervals (DeMauro, Abbasi & Lorch, 2011; Premji & Chessell, 2011) or semi-demand (Watson & McGuire, 2016). DeMauro et al. (2011) reported that VLBW infants with mean birth weight of 1200 gm who were fed at two-hour intervals reached full feedings faster and experienced decreased incidences of feeding intolerance and TPN for shorter lengths

of time compared to those infants fed at three hour intervals. Watson and McGuire (2016) reported that semi-demand feedings were correlated with earlier achievement of full oral feedings, increased nutrient intake and growth rates, and earlier discharge from the NICU by two to four days. In addition, by decreasing the time between feedings, we are decreasing the stretch of the stomach and are meeting the normal GI physiology of stomach volume capacity and gastric emptying of breastmilk (Bergman, 2013). Feeding preterm infants with larger volumes at longer intervals has been associated with increased risk for stress, reflux, and hypoglycemia (Bergman, 2013).

Lastly, the recommended growth standard, 15 gm/kg/day, for one preterm may be sufficient, but a slower trajectory may be more appropriate for a different infant (Embleton et al., 2017). It is possible that if a preterm infant's growth appears stable and is moving appropriately across percentiles and there is no underlying contributing pathology, then quite possibly, this may be optimal (Embleton et al., 2017). Further research studies are needed to address if NICU growth velocity goals should be redefined and how feedings and growth should be managed. The failure of many infants to achieve the desired growth velocity may indicate inadequacy of the current standard.

Limitations

There are two key limitations within this study, including the sampling plan and research design. Nonprobability convenience sampling was used. Generalizability of the findings are limited by the small sample size and use of a single site with a feeding protocol that is not aligned with current practice standards. As a retrospective study, it is not possible to control missing/unrecorded data, errors in documentation, verification of documentation, and reliability of growth measurements obtained and recorded by nursing staff. It is important to consider the

reliability of the growth measures, as they are a direct indicator of the quality of data. There also may be confounding variables that could not be controlled, including perinatal risk factors, postnatal co-morbidities, types/timing of TPN compositions, types and timing of fortification, nutrient composition of maternal/donor milk, and the infant's response to the environment inside and outside of the isolette. These confounding variables can affect the proposed outcome measures. In the future, I would suggest replication of the study utilizing a prospective approach with standardized approach to feeding based on the best evidence. Using an alternative prospective interventional study design would allow the research team to manage the multiple measurement issues described and allow for greater control over possible confounding variables. Training of all NICU staff who perform routine anthropometric measurements should be conducted to monitor and verify the reliability of these measures, both for research and for clinical practice.

Conclusion

Our research findings are consistent with the existing literature that the failure of many infants to achieve the desired growth velocity may indicate inadequacy of the current feeding standards or feeding recommendations. However, in this study sample, suboptimal nutrition management likely contributed to poor quality of growth. Growth failure occurred in this study sample, as evidenced by growth velocity less than 15 gm/kg/day when reaching full enteral feedings. Initiation of human milk fortification or lactoengineering earlier in development may have prevented or decreased extent of growth failure. Lactoengineering, utilizing high fat milk cream from the human milk sample, can provide increased fat and energy content (Hair et al., 2014). Lactoengineering may have a promising future to support an exclusive human milk diet in preterm infants to provide energy-dense feedings without substantial increase in the total volume

of feeds. There is a need for more high quality clinical research to optimize preterm infant nutrition through human milk lactoengineering and fortification.

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Table 1

Participant Characteristics

Variable	Frequency	Percent		
Sex				
Female	38	46.3		
Male	44	53.7		
Type of Gestation				
Single gestation	68	82.9		
Multiple gestation	14	17.0		
Ethnicity				
Caucasian	29	35.4		
Black	43	52.4		
Hispanic	10	12.2		
	Mean	SD	Minimum	Maximum
Diet				
Mother's own milk (MOM), % of total intake	53.69	35.75	0.00	100
Donor human milk (PDHM), % of total intake	20.87	33.03	0.00	100
MOM mixed with PDHM, % of total intake	.08	.70	0.00	6.3
Fortified MOM, % of total Intake	11.62	16.76	0.00	73.49
Fortified PDHM, % of total Intake	6.18	15.31	0.00	65.82
MOM, PDHM, fortified MOM, fortified PDHM, % of total intake	92.46	21.87	0.00	100.00
Formula, % of total intake	7.54	21.87	0.00	100.00
Gestational age at birth, weeks	29.30	3.10	23.70	36.86
Birth weight, gm	1108.80	272.70	530.00	1499.00
Birth length, cm	36.57	3.47	28.00	43.20
Birth head circumference, cm	25.90	2.51	17.50	30.00
Age at first enteral feeding, days	2.07	.72	1.00	5.00

Table 2

Growth Velocity

Participants	Mean	SD	Minimum	Maximum
All Participants (*N* = 82)				
Growth velocity from birth to full enteral feeding (gm/kg/day)	1.71	10.67	-23.37	26.91
Subgroup of infants that reached birth weight prior to full enteral feedings (*n* = 48)				
Growth velocity at time birth weight was regained to full enteral feeding (gm/kg/day)	15.46	6.41	1.25	32.60
Subgroup of infants that experienced fortification (*n*=44)				
Growth velocity from birth to initiation of fortification (gm/kg/day)	3.89	12.76	-35.73	26.62
Growth velocity from birth to full feedings of those infants receiving fortification	0.15	11.09	-23.37	17.72

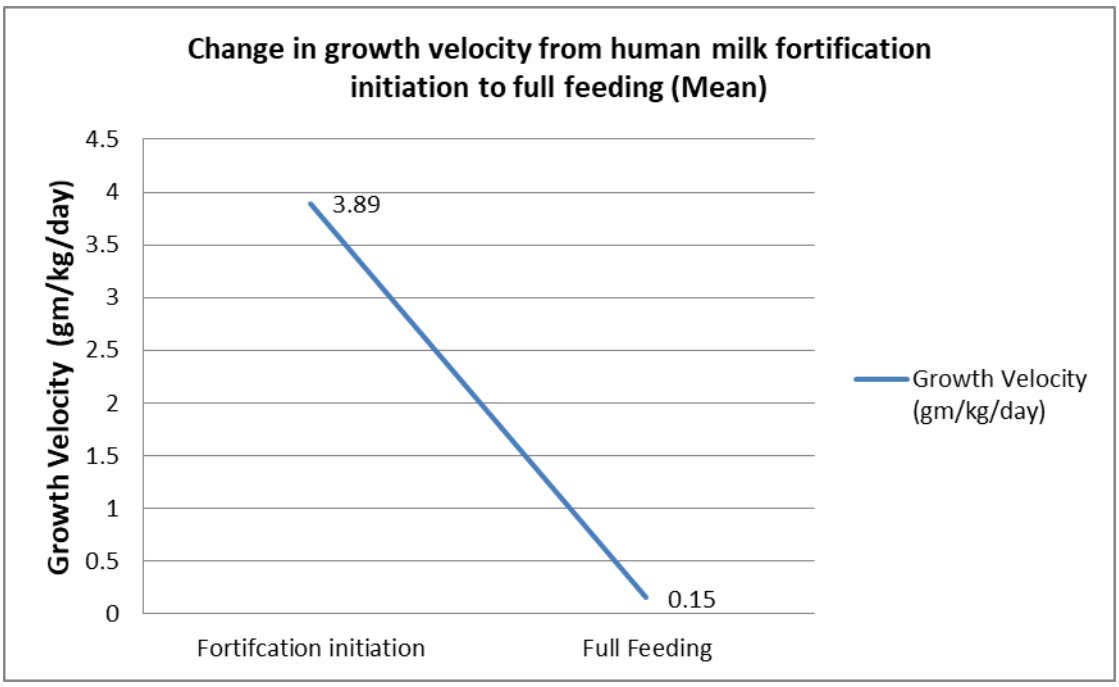

Figure 1. Change in growth velocity from birth to full enteral feeding.

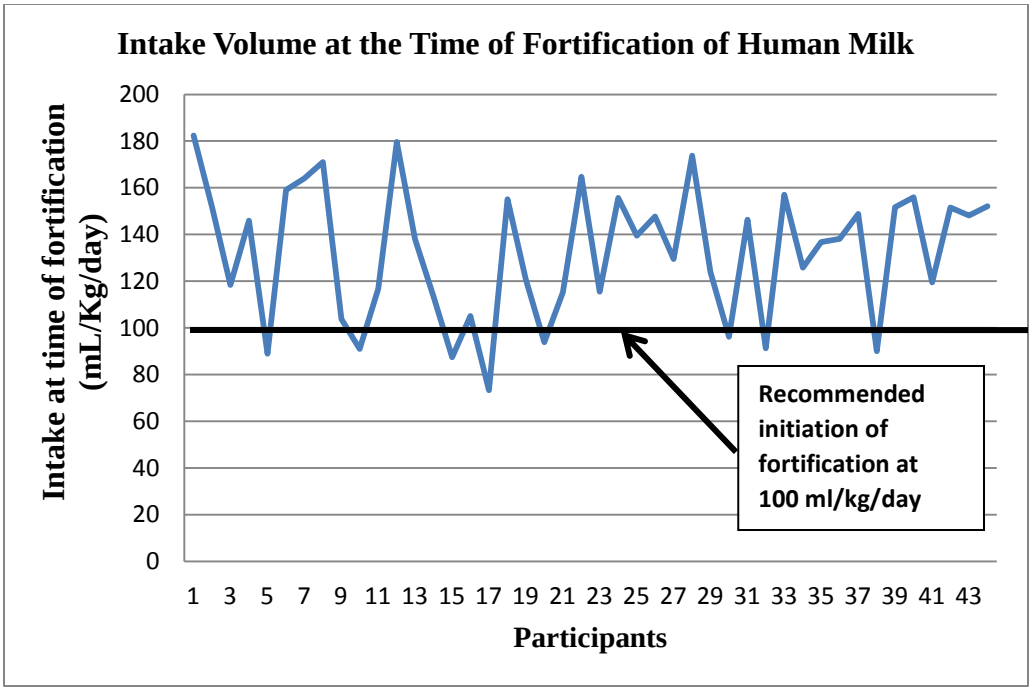

Figure 2. Intake volumes at the time of fortification of human milk.

Chapter VI: Implications for Nursing Practice, Research, and Policy

Chapter VI discusses implications for nursing practice, research, and policy. The section following Chapter VI is the article, "The Political Imperative of an Exclusive Human Milk Diet" submitted and currently under review for publication in the *Journal of Human Lactation*. This manuscript describes and outlines clear recommendations for federal policy expansion of the Affordable Care Act to mandate health insurance company provisions of appropriate coverage of equipment for expression of mother's milk and supply of donor human milk and/or donor human milk-based fortifier to promote and support an exclusive human milk diet for preterm infants.

Implications for Nursing Practice

This study has many implications for nursing practice and for those involved in the care of preterm infants, their growth and development, and the use of human milk, including prescribers, occupational therapists, nutritionists, scientists, and patients. The startling failure of infants to achieve the desired growth velocity of 15 gm/kg/day uncovered in this study may indicate inadequacy of the current growth standards or feeding recommendations, which the entire health care team is failing to address in the NICU setting.

For those nurses working in the United States, fortification of human milk in the NICU has become a standard of care (Spatz, 2017). Brown, Embleton, Harding, and McGuire (2016) performed a meta-analysis examining 14 trials including 1,071 infants and found low quality evidence that fortification during NICU hospitalization increases growth rates of head circumference (mean difference [MD] 0.08 cm/week, 95% confidence interval [CI] 0.04-0.12), length (MD 0.12 cm/week, 95% CI 0.07- 0.17), and weight (MD 1.81 gm/kg/day, 95% CI 1.23-2.40). The expected growth standard in NICUs has remained 0.5 cm to 0.7 cm/week in head circumference, 1 cm/week in length, and 15 gm/kg/day in weight because a superior growth standard has remained undefined (Fenton & Kim, 2013; Greer & Olsen, 2013; Kleinman &

AAP, 2009). It is evident through meta-analysis that the failure of infants to achieve the desired growth velocity with fortification of human milk may indicate inadequacy of the current growth standard (Brown et al., 2016; Spatz, 2017). It is unclear what optimal growth and associated nutrition is for preterm infants. It is possible that if a preterm infant's growth appears stable and is moving appropriately across percentiles, and there is no underlying contributing pathology, then quite possibly this may be optimal (Embleton et al., 2017). It is critical that attention is focused on quality of preterm infant growth, while searching for optimal nutrition composition and management.

What is clearly known is that preterm infants fed an exclusive human milk diet demonstrate improved morbidity compared to formula fed infants (National Breastfeeding Center, 2016). Despite many uncertainties in neonatal growth and nutrition, there is a strong relationship between improved health outcomes and a protective dose response relationship with the duration and/or exclusivity of human milk (Embleton et al., 2017). Currently, use of MOM in the NICU is not prioritized in a manner comparable to other interventional NICU therapies (Meier, Patel, Bigger, Rossman, & Engstrom, 2013). In addition, families and NICU staff have inconsistent education and lactation technologies to optimize duration and exposure of MOM (Meier et al., 2013). Development and utilization of practices and interventions to optimize use of mother's milk should be priority. These practices should include policies and procedures on initiation and frequency of pumping and use of human milk and human milk technologies, utilization of peer counselors, translation of evidence regarding human milk into actionable practices for providers, talking points for staff to ensure information is shared consistently and accurately, and clear messaging that supports human milk as both a source of nutrition and medicine (Meier et al., 2013).

Implications for Further Research

There are multiple opportunities to close the research gap regarding the use of human milk to promote preterm infant growth. In this specific research study, the population was limited to retrospective review, where it was not possible to control for missing/unrecorded data, errors in documentation, and reliability of anthropometric growth measures. There are likely confounding variables that could not be controlled, which include perinatal risk factors, postnatal co-morbidities, types/timing of total parental nutrition compositions, types and timing of fortification, nutrient composition of maternal/donor milk, and the infant's response to their environment inside and outside of the isolette. Follow-up research should include replication of this study utilizing a prospective approach expanding measurement abstraction to include type of fortification, type of pasteurized donor human milk, infant environment (isolette/open crib/phototherapy/kangaroo care), respiratory support, morbidities, daily weights, weekly length and head circumference from birth to hospital discharge with a standardized approach to feeding based on the best evidence. A prospective approach would allow the research team to manage the multiple measurement issues described above and allow for greater control over possible confounding variables.

Further research studies are needed to address if NICU growth velocity goals should be redefined. The risks associated with growth failure or contrary, rapid catch-up growth, has potential health implications that must be weighed heavily when evaluating goal growth standards (Kiger et al., 2016; McLeod et al., 2015; Ong et al., 2000; Sauer, 2007). While some research suggests that catch-up growth is required for preterm infant brain development, others report it is at the possible risk of harmful cardiovascular and metabolic outcomes later in life (Kiger et al., 2016; McLeod et al., 2015; Ong et al., 2000; Sauer, 2007). The current literature on

preterm infant catch-up growth and subsequent increased body fat suggests that the current growth and nutrition recommendations are not effective or safe to achieve normalized body composition postnatally (Kiger at al., 2016). It is possible that lower nutrient intake and slower growth may be protective longitudinally (Embleton et al., 2017). Given the potential for slower growth to affect important outcomes in preterm infants, examining slower growth velocity merits further research. The relationship between fetal and neonatal growth and alteration of subsequent metabolic and cardiac function to prevent risk for harm later in life should be examined. Weight gain by itself may not be adequate to inform the impact and practice of nutrition on growth (Forsum, Olhager & Tornqvist, 2016). Other indices that can inform body composition including ponderal index and BMI, should be further investigated as a parameter of growth in future studies as body composition is predictive of future disease risk (Wells, 2012).

For all disciplines, including nurses, physicians, registered dieticians, and physical and/or occupational therapists, to make clinical decisions regarding use of human milk for preterm infants, they must understand how preterm infant growth is multifactorial based on dynamic interactions between maternal, fetal, and infant physiological, developmental, genetic, nutritional, and environmental factors that can greatly differ between each infant. There are multiple reasons for prenatal and postnatal preterm infant growth failure. Commonly cited reasons for prenatal growth failure include placental insufficiency, fetal programming, maternal inflammation, or infection (Goldenberg, Culhane, Iams, & Romero, 2008). Commonly cited reasons for postnatal growth failure include inadequate nutrition, genetic acquired diseases, physiologic immature organ states, liver disease, endocrine abnormalities, surgery, infection, cold stress, and medications (Bartholomew et al., 2013; Hay, 2013; Hay, Brown, & Denne, 2014; Vinall et al., 2012). The precise mechanism within the maternal and infant systems that influence

individual preterm infant growth failure cannot be established in most cases and is likely a combination of multiple interactions (Goldenberg et al., 2008). Serious commitment to define modifiable risk factors within maternal and infant systems to predict preterm infant growth failure is warranted. The Physiological Growth Model was supported in the literature and the study findings, however, it is a basic foundation that requires further refinement. Other possible prenatal growth factors for preterm infant growth may include mother's weight status and nutritional status. The complexity of growth variables among maternal and infant system has been largely unexplored and is a vast area for future research.

Lastly, there is a need for more high-quality clinical research to optimize preterm infant nutrition through human milk lactoengineering. Lactoengineering, utilizing high fat milk cream from the human milk sample, can provide increased fat and energy content (Hair et al., 2014, Ogechi et al., 2007, Slusher et al., 2003). Lactoengineering may have a promising future to provide energy dense feedings without substantial increase in the total volume of feeds. Given the potential of lactoengineering to support an exclusive human milk diet that is genetically engineered for each individual infant and subsequent effects on important outcomes in preterm infant growth and health, this intervention merits further research. An exclusive human milk diet is associated with decreased risk of NEC, respiratory infection, sepsis, and overall survival (Palmer, 2015). Interventional studies comparing different preparations of high fat milk cream, powered to detect important effects on growth rates and adverse events, including NEC, in preterm infant hospitalization and beyond, should be designed. The protocols used for lactoengineering and creamatocrit measurements should be published. In addition, investigators should examine the effects of lactoengineering compared to use of human milk based fortifier to determine if it provides cost effective advantages during preterm infant hospitalization.

The Political Imperative of an Exclusive Human Milk Diet in Preterm Infants

Abstract

The United States is well overdue for a federal mandate of insurance companies to cover a different type of medicine for preterm infants—human milk. For nearly all infants, human milk is the superior and preferred food. Human milk is not only a fundamental basic need, but it can be a lifesaving food and medicine for medically fragile preterm infants. Anti-inflammatory and anti-infective properties specific to human milk, which are not found in formula, can help prevent serious or fatal health conditions in preterm infants. However, preterm infants who benefit greatest from consuming human milk may have the most difficulty receiving it. The associated costs in providing human milk can lead to inequitable access to an exclusive human milk diet for many preterm infants and contribute to breastfeeding disparities. The purpose of this manuscript is to describe and outline clear recommendations for federal policy expansion of the Affordable Care Act to mandate health insurance company provisions of appropriate coverage of equipment for expression of mother's milk and supply of donor human milk and/or donor human milk-based fortifier to promote and support an exclusive human milk diet for preterm infants.

Background

The United States is well overdue for federal mandate of insurance companies to cover a different type of medicine for preterm infants—human milk. For nearly all infants, human milk is the superior and preferred food. Human milk has immunologic benefits that offer health protection and disease reduction across the lifetime for infants and mothers (U.S. Department of Health and Human Services, 2011). A minimum of $13 billion dollars in medical expenses and 911 infant deaths per year could be saved if 90% of families in the United States breastfed

exclusively for six months, with continued breastfeeding to one year old (Bartick & Reinhold, 2010).

Worldwide, approximately one million children die annually due to complications of preterm birth (Liu et al., 2016). Preterm birth is defined as those infants born before 37 completed weeks gestation. Globally, preterm infant birth is a significant problem, with increasing preterm infant birth rates in almost all countries that report preterm infant birth rates (World Health Organization [WHO], 2018). In 2017, the preterm infant birth rate rose for the third year in a row to 9.93% in the United States (Hamilton, Martin, Osterman, Driscoll & Rossen, 2018). The United States is ranked sixth of 10 countries that account for the highest number of preterm births annually (Blencowe et al., 2012).

Human milk can be a lifesaving food and medicine for medically fragile preterm infants. Anti-inflammatory and anti-infective properties specific to human milk, which are not found in formula, can help prevent serious or fatal health conditions in preterm infants. However, preterm infants who benefit greatest from consuming human milk may have the most difficulty receiving human milk. Barriers to preterm infants receiving human milk may include a maternal disease/ surgery/death, maternal use of drugs or certain medications, inadequate or no milk available, and associated costs. The associated costs in providing human milk can lead to inequitable access to an exclusive human milk (EHM) diet for many preterm infants.

Providing human milk for preterm infant nutrition is a matter of women and infant health that should be accessible and affordable for all who desire to utilize it. A federal mandate of health insurance coverage to provide appropriate equipment for expression of mother's milk and supply donor human milk and donor human milk-based fortifier is a fundamental basic need for preterm infants. The purpose of this manuscript is to describe and outline clear recommendations

for federal policy expansion of the Patient Protection and Affordable Care Act (ACA, 2010) to mandate health insurance company provisions of appropriate coverage of equipment for expression of mother's milk and supply of donor human milk and/or donor human milk-based fortifier to promote and support an EHM diet for preterm infants. As the ACA currently stands, the specific needs for human milk and preterm infants is not addressed.

Despite historic health reform in the ACA (2010) to include provisions to support breastfeeding, the current state of the ACA represents a disconnected patchwork rather than a unified direction towards eliminating breastfeeding disparities for preterm infants (Hawkins, Dow-Fleisner & Noble, 2015). Disparity exists when there is a difference in access and opportunity to healthcare that results in differences in underlying health (Jones, Jones, Perry, Barclay & Jones, 2009). As it currently stands, the ACA provides health insurers the power to decide, act, and control supply of human milk for preterm infants that can subsequently result in decreased spending on breastfeeding support. A recent example includes Anthem Blue Cross Blue Shield's decision, effective April 1, 2018, to cut coverage of breast pumps by 45%, from $169 to $95 (United States Breastfeeding Committee, 2018). Anthem Blue Cross Blue Shield provides insurance coverage of over 40 million Medicaid enrollees, a specific group that includes low income families. This decision to decrease reimbursement to improve profits was a cut in breastfeeding support that further fuels breastfeeding disparity (United States Breastfeeding Committee, 2018).

Limitations of the Affordable Care Act and Breastfeeding Preterm Infants

A major provision in the ACA (2010), Section 2713 Women's Preventative Service, requires health plans to cover costs associated with providing human milk to infants. This provision requires health plans to cover breastfeeding supplies, including breast pump rental or

purchase and breastfeeding counseling/educational services (ACA, 2010). Within this provision, there lacks clear language or guidelines as to the type of equipment that should be covered, and as a result, there are extreme inconsistencies in equipment coverage and disrupted continuity of breastfeeding services, which can result in failure to supply human milk for those in need (National Breastfeeding Center, 2016).

Mothers of preterm infants commonly require a hospital-grade electric breast pump to initiate and support milk supply. Mothers of preterm infants should initiate pumping with a hospital-grade breast pump within six hours postpartum, with minimum of eight pumping sessions daily, to protect future milk production potential (Stanford Medicine, 2017). Under current ACA provisions, approximately 23% of insurance companies do not cover this type of pump (Medela, 2013). Some insurers only cover a manual hand pump, which is not adequate to establish or maintain milk supply when a mother is separated from her infant or unable to feed directly from the breast, as is many times the case for preterm infants (National Breastfeeding Center, 2016). The remaining 77% of insurance companies that provide insurance coverage of electric-grade pumps may require preauthorization, which can take days or even weeks after the birth of the infant to obtain (Medela, 2013; National Breastfeeding Center, 2016).

Lastly, for those mothers of preterm infants who are unable to provide mother's milk, donor human milk is a great alternative that offers similar health protections to mother's milk (Vongbhavit & Underwood, 2016). Carroll and Herrmann (2013) reported that 72% of mothers of very preterm infants in the NICU were unable to provide all mother's milk needed for an EHM diet. Hospitals that use banked donor milk generally have minimal budgets allocated for purchase of donor milk (National Breastfeeding Center, 2016). Donor human milk costs, on average, $4.50 per ounce; however, for every $1.00 spent on donor milk, there is a potential

saving up to $11.00 in medical costs of the preterm infant (Huertas, 2015). The ACA does not address coverage of donor milk.

Mother's milk and donor human milk may not always meet the high nutrient needs of preterm infants without fortification (Schanler, Lau, Hurst, & Smith, 2005). Fortification of human milk provides increased protein and is correlated with exceeding expected growth velocity and improving weight gain and linear growth (Reali et al., 2015; Rochow et al., 2013). The American Academy of Pediatrics (2012) recommends that all human milk should be fortified with protein, minerals, and vitamins in preterm infants weighing less than 1,500 grams at birth.

The two primary types of fortification include donor human milk-based fortifier or a bovine milk-based fortifier. Bovine fortifier is the most commonly used fortifier in NICUs due to immediate upfront cost. However, use of a bovine fortifier in human milk exposes the infant to non-human milk protein and is associated with possible serious health issues, including increased risk of necrotizing enterocolitis (NEC), respiratory infection, sepsis, and overall reduced survival (Underwood, 2013).

The potential long-term cost savings by adhering to an EHM diet and avoiding bovine fortifier is profound among extremely preterm infants in the NICU. In avoidance of NEC alone, Ganapathy, Hay, and Kim (2012) reported a lower expected NICU length of stay of 3.9 NICU days and net direct average savings of $8,167.17 per extremely premature infant ($p < 0.0001$) fed EHM diet compared to those infants fed a bovine fortified diet. Since there is no federal regulation requiring insurance coverage of donor human milk-based fortifier, it remains significantly underutilized.

Recommendations

Development of Policy Expansion

No infant should be exposed to suboptimal nutrition. Surviving preterm infancy should not be constrained by cost or maternal supply limitations. To specifically address support and delivery of an EHM diet for preterm infants, clear policy recommendations for provision expansion of section 2713 Women's Preventative Services in the ACA (2010) or other future replacement policies are proposed. The three primary areas for provision expansion are coverage of breastfeeding pumps and supplies, coverage of donor milk, and coverage of donor human milk-based fortification. These areas of provision expansion are economically driven and provide substantiated health benefits for mothers and infants. These recommendations are supported by policy statements from the WHO (2018) recommending standard nutrition practices in NICUs to promote mother's milk first, followed by donor human milk when mother's milk is unavailable (Krolak-Olejnik & Czosnykowska-Lukacka, 2017). These areas for provision would require health plan coverage of services and supplies that align with recommended best nutrition practices for preterm infants.

Breastfeeding Pumps and Supplies

Breast pump coverage is to include a dual electric-grade breast pump with a breast pump kit (tubing, valves, flanges, collection bottles, and other parts as specified by the manufacturer) for use of mothers of preterm infants for the first year of the child's life. Up to 16 human milk storage bags per day would be covered to allow for expression and storage of human milk every three to four hours. An electric-grade breast pump should be made available within 24 hours of notification of need (National Breastfeeding Center, 2016), with no cost sharing to the member.

Donor Human Milk

In cases when mother's milk is not available, banked donor human milk is the first choice for preterm infants. Pasteurized donor milk, provided from an approved Human Milk Banking Association of North America milk bank, will be a covered benefit for preterm infants (National Breastfeeding Center, 2016). Prescription from a licensed provider that identifies the medical diagnosis and necessity and 3-month renewal of the prescription will be required (National Breastfeeding Center, 2016). The covered benefit will include infants from birth to 12 months of age, when decided by a medical provider that it is medically necessary (National Breastfeeding Center, 2016), with no cost sharing to the member.

Donor Human Milk-Based Fortifier

In cases when fortification of mother's milk or donor human milk is required, as identified by a medical provider, human milk-based fortifier will be a covered benefit. Prescription from a licensed provider that identifies the medical diagnosis and necessity will be required, along with a 3-month renewal of the prescription. The covered benefit will include infants from birth to 12 months of age, when decided by a medical provider that it is medically necessary, with no cost sharing to the member.

Conclusion

Mothers and preterm infants need uncompromised and high quality breastfeeding support. Providing an EHM diet to vulnerable preterm infants can make a lifesaving difference and provide large economic healthcare cost savings. As it currently stands in the ACA (2010), the lack of coverage of appropriate breast pumps and supplies, donor human milk, and human milk-derived fortifier leads to inequitable access for an EHM diet for preterm infants. The outlined federal policy expansion would provide landmark legislation designed to improve the

quality, delivery, and efficiency of providing human milk for preterm infant feeding in the United States. These recommended approaches to policy change are greatly needed to address breastfeeding as a national priority (Hawkins et al., 2015). It is imperative that in discussion of repeal and replacement of the ACA, consideration for breastfeeding expansion address preterm infant nutrition. It is now time to call on policymakers, lobbyists, healthcare providers, and stakeholders to advocate for these provisions and make legislative efforts to ensure equitable comprehensive access of human milk for all preterm infants.

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CURRICULUM VITAE

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EDUCATION

Doctoral Candidate in Nursing Science. Anticipated Graduation: December 2018
University of Wisconsin Milwaukee. Milwaukee, Wisconsin
Dissertation: *Preterm Infant Growth and Human Milk Exposure in the NICU*

Master of Science in Nursing. Graduation: May 2012
University of Wisconsin Oshkosh. Oshkosh, Wisconsin
Emphasis: Family Nurse Practitioner

Bachelor of Science in Nursing. Graduation: May 2010
University of Wisconsin Oshkosh. Oshkosh, Wisconsin
Minor: Women's Studies

CLINICAL EXPERIENCE

Divine Savior Healthcare Portage, Wisconsin
Nurse Practitioner, Obstetrics and Gynecology, August 2017 – present

Divine Savior Healthcare Portage, Wisconsin
Nurse Practitioner, Family Practice, October 2012 – August 2017

Mercy Medical Center Oshkosh, Wisconsin
Registered Nurse, Inpatient Pediatrics, June 2010 – November 2014

St. Elizabeth Hospital Appleton, Wisconsin
Registered Nurse, Women and Families, June 2010 – November 2014

PUBLICATIONS

Schehr,L. & Johnson, T.S. (2018). Preterm Infant Growth and Human Milk Exposure in the NICU Abstract. *Breastfeeding Medicine,13*(7), P-122.

Schehr, L., & Johnson, T.S. (2017). Concept Analysis of Growth Failure in Preterm Infants in the NICU. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 46*(6), 870-877.

PRESENTATIONS

Schehr, L., & Johnson, T.S. "Preterm Infant Growth and Human Milk Exposure in the NICU (Poster)." 19th Conference of International Society for Research in Human Milk and Lactation. Kanagawa, Japan. October 2018.

Schehr, L. "A Concept Analysis of Premature Infant Growth Failure (Poster)." Experimental Biology Conference. Chicago, Illinois. April 2017.

AWARDS/GRANTS

- Breastfeeding Coalition of South Central Wisconsin Healthcare Award, April 2018
- CTSI Biostatistical Grant, March 2018
- ISRHML Trainee Travel Award, June 2018
- University of Wisconsin Milwaukee Dean's Scholarship Recipient, February 2015
- Willcockson Scholarship Award Recipient, September 2011
- University of Wisconsin Oshkosh Dean's Scholarship Recipient, August 2011
- President's Promise Award Recipient at Affinity Health System, May 2010

PROFESSIONAL ACTIVITIES

- Association of Women's Health, Obstetric, and Neonatal Nurses Member, October 2015-present
- International Society for Research in Human Milk and Lactation Trainee, October 2015-present
- Wisconsin Nurses Association Member, May 2015- present
- American Nurses Association Member, May 2015- present
- Sigma Theta Tau National Honor Society Member, February 2010- present
- Interview Committee Member for the Tenure Track Employees at University Of Wisconsin Oshkosh, September 2011

CERTIFICATIONS

- Neonatal Resuscitation Program, Expires: June 2019
- CPR/AED Certified, Expires: May 2019
- Certified Lactation Counselor, September 2014
- Private Pilot Certification, May 2009